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Physical urticaria

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Chronic urticaria can occur through a variety of mechanisms, including allergic, cytotoxic, autoimmune, and idiopathic mechanisms, which are waiting to be defined. Patients with physical urticarias make up a subset of those with chronic urticaria. These individuals have urticaria that is induced by a wide variety of environmental stimuli, such as exercise, temperature changes, cold, heat, pressure, sunlight, vibration, and water.

Chronic urticaria afflicts approximately 20% of people at some point in their lifetimes, and most of these cases are idiopathic in origin. Physical urticarias are responsible for approximately 20% to 30% of cases of chronic urticaria. In some patients, the physical stimuli are the predominant cause of the condition, whereas in other patients it is an incidental factor in a case of chronic idiopathic urticaria. A small number of patients have multiple physical urticarias at the same time.

This article covers the following types of physical urticarias: dermatographism, cholinergic urticaria, local heat urticaria, exercise-induced anaphylaxis, vibratory angioedema, solar urticaria, and aquagenic urticaria. Cold urticaria and delayed-pressure urticaria are discussed in articles elsewhere in this issue.

Dermatographism

Dermatographism (also referred to as dermographism or urticaria factitia) literally means to ''write on the skin.'' Patients with this condition develop the rapid onset of a cutaneous wheal and flare after experiencing skin pressure. It is the most common of the physical urticarias and is often an incidental finding in the evaluation of other skin conditions, most commonly atopic dermatitis, chronic idiopathic urticaria, and the other physical urticarias discussed in this article.

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There are several forms of dermatographism. Most individuals have simple dermatographism, which is asymptomatic. The other forms of dermatographism are symptomatic and vary in their clinical appearances.

Epidemiology

Simple dermatographism is the most common variant and is estimated to occur in approximately 2% to 5% of the general population [1,2]. The symptomatic forms of dermatographism are much less common, and no prevalence data have been established. There is a single case report of familial dermatographism [3].

Clinical features

In simple dermatographism, an erythematous wheal is provoked by stroking the skin with a firm object. The wheal typically appears within 6 to 7 minutes and begins to fade 15 to 30 minutes later [1]. The lesions of symptomatic dermatographism are slightly different, appearing in less than 5 minutes and lasting 30 minutes [4]. There are also intermediate and delayed forms of dermatographism (likely synonymous with delayed-pressure urticaria) that develop more slowly and can last several hours to several days [4]. Patients with these forms often describe burning and pain in addition to pruritus. Patients with delayed-pressure urticaria may develop arthralgias associated with their urticaria [5].

In addition to classic wheals, variants of symptomatic dermatographism have been described in which the reactions are follicular [6] or inflamed and swollen (red dermatographism) [7].

Although a purposeful stroking of the skin is the most common way to elicit symptoms, patients often are unaware of the inciting event. Occasionally, idiopathic pruritus or pruritus caused by dry skin can be the event that elicits scratching and subsequent dermographism. In this setting, the wheals are typically linear. Simple actions such as scratching, leaning against a solid object, or irritation from clothes or bed sheets may provoke whealing. In one case series, dermatographism could be exacerbated by hot water, emotion, exercise, or cold exposure [8].

In most patients, dermatographism is idiopathic without a clear inciting event. Cases have been described in which symptomatic dermatographism was triggered by infections with bacteria, fungi, and scabies [5,9] and after receiving penicillin [10] or famotidine [11].

Pathogenesis

The pathogenesis of dermatographism remains uncertain. Elevated levels of serum histamine have been demonstrated after a whealing episode [12]. There have been successful passive transfer experiments in which serum from a dermatographic patient transferred dermatographism to a monkey [12,13]. These experiments suggest an IgE-mediated reaction, but no allergen has been identified.

Diagnostic testing

Patients with dermatographism can be diagnosed in an office setting by stroking the skin with a firm object, such as a tongue blade. This action provokes a typical wheal-and-flare response within a few minutes, as described earlier. Care should be exercised to be sure that the patient is not taking antihistamines.

In a controlled environment such as a research setting, a device called a dermographometer can be used to apply a well-defined, reproducible amount of pressure to a subject's skin. This device is also useful in documenting a response to therapy. The threshold for eliciting a response in simple dermatographism is 4900 g/cm^2, whereas in symptomatic dermatographism the threshold is 3200 to 3600 g/cm^2 [1,4,14]. The dermographometer may be used in the diagnosis of delayed-pressure urticaria. Unlike in dermatographism, where a response is elicited within a few minutes, patients with delayed-pressure urticaria manifest symptoms several hours after a challenge. In both conditions, patients may respond to a variable amount of applied pressure, but the onset of symptoms distinguishes immediate-onset dermatographism from delayed-pressure urticaria. Although dermographometers occasionally are referenced in research protocols, the author was unable to locate one for purchase, suggesting that the average physician should rely on the simple in-office techniques described earlier.

Treatment

Simple dermatographism is asymptomatic and requires no therapy. Treatment of symptomatic dermatographism includes avoidance of any inciting triggers and the use of medications. If wheals are provoked by scratching because of dry skin, the use of proper skin hydration and emollients can improve the symptoms. H_1 antihistamines have been shown to be effective in dermatographism and are the initial drug of choice. Earlier studies demonstrated a significant improvement with the first-generation antihistamines, particularly hydroxyzine [7,15,16]. Several investigators have reported that the addition of an H_2 antihistamine is beneficial [16–18], whereas others have failed to show improvement over use of H_1 antihistamines alone [12]. Juhlin et al demonstrated that the second-generation H_1 antihistamine cetirizine provided significant benefit in controlling symptoms [19]. In some patients, sun exposure improved their condition, and studies have demonstrated that exposure to ultraviolet B (UVB) light can be effective [20].

Cholinergic urticaria

Cholinergic urticaria is the name given to hives that are precipitated by an increase in core body temperature. The condition occasionally is referred to as generalized heat urticaria. Common triggers include exercise, strong emotions, and bathing in hot water. Cholinergic urticaria first was described in 1924 by Duke in a patient who experienced hives after exercising, experiencing strong

emotions, and applying heat to the skin [21]. In 1936, Grant reported six patients with a similar presentation [22]. Grant postulated that these hives were caused by the cholinergic nervous system.

Epidemiology

Cholinergic urticaria is believed to account for approximately 5% of all cases of chronic urticaria [23] and approximately 30% of all cases of physical urticaria. About 15% of the population will experience at least one episode at some point in their lives [8]. Cholinergic urticaria typically has its onset during the second or third decade of life [24–26]. Whereas one study noted a predominance in male patients [24], others have found that both sexes are affected equally [25,26]. Familial cases are rare but have been reported [27]; in these cases, all affected patients were male.

Clinical features

The classic initial appearance of cholinergic urticaria is that of numerous punctate wheals (1–3 mm) surrounded by large flares. Many patients note a tingling, itching, or burning sensation of the skin before the appearance of the hives [24]. As the response progresses, the flares may coalesce to form large areas of erythema that become more difficult to recognize as cholinergic urticaria. The wheals typically begin on the trunk and neck and spread distally to involve the face and extremities, although lesions may begin anywhere on the body. In rare cases, cholinergic urticaria has been reported to progress to include systemic symptoms such as hypotension, angioedema, and bronchospasm [22,24,28].

As mentioned earlier, any trigger that results in an elevation of core body temperature may provoke the onset of cholinergic urticaria. Exercise is one of the most common triggers, and cholinergic urticaria may be confused with exercise-induced anaphylaxis if other triggers are not excluded. Other typical inciting factors include hot baths or showers, strong emotional feelings, and ingestion of spicy or hot foods [24,25]. All of these factors also lead to increased sweating, which may have some bearing on the pathogenesis of the condition.

In one study, a patient with preexisting cholinergic urticaria experienced a flare of his condition while undergoing dialysis treatments [29]. A decrease in the patient's dialysate temperature by 1.5°C led to resolution of his symptoms. Rechallenge with fluid at a higher temperature reproduced his urticaria.

Cholinergic urticaria must be differentiated from exercise-induced anaphylaxis, which is discussed later in this article. Whereas cholinergic urticaria may be triggered by a variety of factors, exercise is a prerequisite for the development of exercise-induced anaphylaxis. The hives of exercise-induced anaphylaxis are typically larger in size than those of cholinergic urticaria, although there is a variant of anaphylaxis that presents with punctate lesions. Although these hives look identical to those of cholinergic urticaria, they only appear with exercise and not with any other triggers that elevate core body temperature.

Pathogenesis

The underlying mechanism of cholinergic urticaria has not been elucidated fully, but it generally is believed to involve an abnormal cutaneous response in the presence of cholinergic agents. Elevated levels of histamine have been detected in the serum during an attack [28]. Patients with this condition have been shown to have an increased number of muscarinic receptors in areas that demonstrate hives [30]. A neurogenic reflex may be involved, as application of a tourniquet proximal to a site of increased heat exposure has been shown to eliminate the whealing reaction [31].

The presence of a more typical antigen–antibody reaction also has been investigated. Murphy et al performed passive transfer experiments using sera from patients with cholinergic urticaria that were injected into the skin of a primate [32]. When the monkey was injected with acetylcholine, a cutaneous reaction was observed with 7 of 16 patient sera. This finding seemed to suggest that a transferable serum factor exists in at least some patients with cholinergic urticaria. Adachi et al reported a group of patients who seemed to have a type I allergy to their own sweat [33]. Twenty patients underwent autologous sweat testing and demonstrated an immediate skin reaction. A subgroup of patients with symptoms suggestive of cholinergic urticaria may have allergic urticaria that is manifest only when they sweat.

There have been several reports of patients with cholinergic urticaria that is associated with hypohidrosis [34,35]. Kabayashi et al postulated that occlusion of the pores of the stratum corneum could cause hypohidrosis and subsequent leakage of inflammatory sweat materials into the upper dermis, resulting in a whealing reaction [35].

As with many other physical urticarias, a variety of pathogenetic mechanisms have been demonstrated or postulated in cholinergic urticaria, and there may be different mechanisms at work in different patients.

Diagnostic testing

The presentation of the lesions of classic cholinergic urticaria in the context of typical inciting triggers is often enough to strongly suggest the diagnosis, but confirmatory testing should be conducted. Confirmation is done by provocation testing using a variety of methods.

Classically, the methacholine injection should be positive in patients with cholinergic urticaria. An intradermal injection of 0.01 mg of methacholine in 0.1 mL saline produces a local area of hives and is diagnostic. Only about one third of patients with cholinergic urticaria demonstrate a positive test, however [24,36]. This procedure cannot be used to rule out the diagnosis.

Specific provocative challenges may be needed and may use the inciting event suspected in a particular patient. These challenges could include exercise, bathing, or ingestion of certain foods. These tests may not be specific enough, however, as they overlap with other causes of urticaria: exercise-induced anaphylaxis, aquagenic urticaria, and food hypersensitivity, respectively.

The best diagnostic test is one that measurably raises the patient's core body temperature. To that end, a patient should be submerged partially in a hot water bath at 40°C until the core body temperature has increased at least 0.7°C [36]. Under these conditions, the appearance of generalized urticaria confirms the diagnosis of cholinergic urticaria. Aquagenic urticaria may be precipitated by this procedure but can be differentiated, as these wheals should occur only on the submerged portions of the skin.

Treatment

Identification and avoidance of known triggers are the first steps in controlling cholinergic urticaria. Bathing in hot water and performing strenuous exercise during hot weather are to be avoided. Medical therapy is predominantly oral antihistamines. Hydroxyzine is the classic agent of choice [2] and generally is believed to be more effective than other antihistamines [25]. A low dose should be initiated and increased gradually until the urticaria is controlled, which typically occurs at doses of 100 to 200 mg divided over 24 hours. Oral anticholinergic agents have not been shown to be effective [25]. Ketotifen has been shown to improve the symptoms of cholinergic urticaria. [37,38].

Wong et al demonstrated that the anabolic steroid danazol could be effective [39]. This agent is postulated to correct the low blood levels of protease inhibitors that occur in some patients with cholinergic urticaria [40]. Given its potential for adverse effects, however, this medication should be reserved only for severe cases refractory to antihistamines.

Beta-blocker therapy occasionally has been recommended for certain cases because of its anxiolytic effects [8]. One case report demonstrated efficacy of propranolol in a patient with only exercise-induced symptoms [41]. This class of medication should be used only with extreme caution in patients who might be predisposed to anaphylactic symptoms.

Moore-Robinson and Warin reported that a period of latency was induced after an episode of cholinergic urticaria [25]. In most cases, these relatively symptom-free periods lasted only a few hours but could last more than 24 hours if the initial episode was severe. The authors also described two patients who treated themselves on a nightly basis using a dose of antihistamine that was followed 3 hours later by a hot bath. This desensitization regimen was successful in helping to control their symptoms.

The prognosis for cholinergic urticaria is generally favorable. Hirschmann reported only 31% of patients with persistence of symptoms greater than 10 years [24]. Sibbald estimated that the average duration of symptoms is 7.5 years (range, 3–16 years) [42].

Local heat urticaria

In addition to the generalized form of heat urticaria (cholinergic urticaria), there is also a rare localized form that warrants a brief mention. In local heat

urticaria, a warm stimulus must come into direct contact with the skin and result in the formation of a wheal within minutes [31]. There is one case report of a familial, delayed-type variant of local heat urticaria [43]. The pathogenesis involves histamine release, implicating the mast cell in the cause of this condition [44]. Passive transfer experiments, however, have been negative.

Diagnostic testing is conducted by the application of a test tube containing water at 44°C to the arm for 4 to 5 minutes [31]. Other authors recommend using a cylinder heated to 50°C to 55°C [14]. A localized hive should develop within a few minutes after removal of the heated object if local heat urticaria is the true diagnosis.

Therapy using antihistamines and oral cromolyn has not been effective [31]. Desensitization using hot baths was successful in one patient but carries with it the risk for a systemic reaction [45].

Exercise-induced anaphylaxis

Urticaria with exercise has been shown to occur in two distinct situations. The first situation is in patients with cholinergic urticaria. As previously described, these patients develop urticaria after exercising and after experiencing any other trigger that elevates core body temperature. The second situation is in patients with exercise-induced anaphylaxis in which urticaria is an early manifestation of true anaphylaxis. Unlike in cholinergic urticaria, exercise is the only trigger in exercise-induced anaphylaxis. Whereas systemic symptoms are uncommon in cholinergic urticaria, they are expected in exercise-induced anaphylaxis if the patient continues to exercise through the early manifestations.

The condition first was described in 1979 by Maulitz et al in a patient with an anaphylactic response to shellfish that was precipitated by exercise [46]. Since then, exercise-induced anaphylaxis has been described as an isolated entity but also in association with food ingestion, medication use, and menstruation [47]. Reports of exercise-induced anaphylaxis have been increasing, an observation that usually is explained by the increasing popularity of exercise and physical conditioning.

Epidemiology

Wade et al conducted a questionnaire survey of 199 patients with exercise-induced anaphylaxis [48]. Age of onset ranged from 4 to 74 years (mean, 24.7 years). Some patients had experienced frequent, recurring episodes, whereas others reported only a single event. Shadick et al [49] conducted a similar survey and identified 279 patients with symptoms consistent with exercise-induced anaphylaxis. They found similar age ranges as the previous study but also noted that females made up 71% of the patient population. In both studies, approximately 50% of patients had a personal history of atopy. The medical literature

contains more than 1000 reports of patients with exercise-induced anaphylaxis, but only one death has been reported [50]. Despite the large number of reported cases, only two cases with a familial pattern have been reported [51,52].

Clinical features

Shortly after Maulitz' case report, Sheffler and Austin recognized exercise-induced anaphylaxis as a distinct clinical entity, and their description of 16 patients with the condition is still an ideal description of the clinical presentation [53]. Within several minutes of exercising, patients experience a prodromal phase characterized by fatigue, warmth, pruritus, and erythema. These symptoms progress to large hives that become confluent and eventually appear as angioedema. If exercise is maintained, the attack develops into systemic anaphylaxis with cardiovascular (hypotension, syncope), respiratory (wheezing, stridor), and gastrointestinal (colic, nausea, vomiting) symptoms. Once fully developed, the attacks last 30 minutes to 4 hours. A late phase has been described that manifests as headache, fatigue, and warmth and could last from 24 to 72 hours.

Exercise-induced anaphylaxis may be triggered by any physical activity but most commonly is triggered by jogging, brisk walking, dancing, and aerobic sports [49]. Even mild activities have been shown to induce an attack; patients reported symptoms from yard work, horseback riding, shoveling snow, and skiing [49]. Reactions in exercise-induced anaphylaxis tend to be variable in occurrence and often are not reproducible despite engaging in the same activity that previously provoked a severe reaction. Other factors that have been associated with exercise-induced anaphylaxis include menstruation [48], use of aspirin and nonsteroidal anti-inflammatory drugs [49], and exposure to cold weather [54].

Sheffler and Austen have described a variant type of exercise-induced anaphylaxis in which patients present with punctate wheals rather than the larger variety [55]. These wheals appear identical to those found in cholinergic urticaria but are triggered only by exercise and not by elevations in core body temperature. This variant seems to be found in approximately 10% of cases of exercise-induced anaphylaxis [56].

A group of patients has been characterized as having food-dependent, exercise-induced anaphylaxis. These patients require exercise and the ingestion of a specific food (or, in some cases, any solid food [57,58]) to provoke an anaphylactic reaction. Neither exercise by itself nor ingestion of the food by itself is sufficient to cause the reaction. Patients who react to a specific food seem to have a type I–mediated process, as prick skin tests for the culprit food are usually positive. Patients who react with the ingestion of any solid food and are skin tested with suspected culprit foods will have negative tests thereby demonstrating a lack of specific IgE.

In most cases, exercising within 3 hours of ingestion of the culprit food leads to a reaction. Kidd et al described a patient who exercised first and then developed an anaphylactic reaction after eating celery [57]. The list of foods implicated in this condition continues to grow and, in addition to the previously

mentioned shellfish [46] and celery [57], now includes chicken, hazelnut, apples, peaches, grapes, wheat, grain flours, and cabbage [49,59–66].

Pathogenesis

The role of the mast cell in exercise-induced anaphylaxis has been supported by studies that demonstrate elevations in levels of serum histamine [67] and tryptase [68] during attacks. There is also histologic evidence of mast cell degranulation seen on skin biopsies taken immediately after an attack [69]. The cause of the mast cell degranulation remains uncertain. Some researchers have postulated that the reactions may be IgE mediated [67,70]. Because exercise is a prerequisite for an attack to occur, an allergen may be released during physical exertion.

A priming phenomenon may be at work [71], with food, medications, or other stimuli acting as necessary cofactors for the reaction to occur. Conversely, exercise occasionally may be the priming factor for a food or other trigger. The priming factor in reactions that seemingly are caused by exercise alone is unknown, but this concept could explain why reactions in exercise-induced anaphylaxis are so variable in occurrence. The presence, intensity, or duration of the cofactor (or cofactors) could be critical in determining the initiation or severity of the subsequent reaction.

Diagnostic testing

Exercise testing is the method of choice for diagnosing exercise-induced anaphylaxis. Passive warming tests to rule out cholinergic urticaria with systemic symptoms may be necessary. Exercise testing must be done under controlled conditions with medical personnel, epinephrine, and resuscitative equipment available for emergencies. Vital signs and spirometry should be monitored, although this monitoring may be difficult during certain exercises. Placement of an intravenous catheter to draw serum markers and possibly administer medications is highly recommended. Patients generally exercise by running on a treadmill or using a stationary bicycle with incremental increases in exertion. Free running or another natural activity is an option but offers a much less controlled environment.

As previously mentioned, exercise-induced anaphylaxis is often difficult to reproduce, and false-negative challenges are common. Testing may need to be repeated on multiple occasions to prove the diagnosis.

Treatment

The first step in effective management of exercise-induced anaphylaxis is to identify and avoid any specific foods, medications, or other associated factors. Patients may be required to limit the frequency or intensity of their activities; at the least, they must be educated to change their behavior when it comes to exercise. They should carry self-injectable epinephrine at all times, exercise with a partner who is trained to use epinephrine, and avoid exercising within 4 to 6 hours of

eating. Because the pathogenesis of exercise-induced anaphylaxis and food-associated exercise-induced anaphylaxis remains unclear, it may be advisable to have all patients avoid eating before exercise, not just those with a known food trigger. Some patients can reduce the number of attacks by not exercising during extremely hot, humid, or cold weather or during an allergy season [49].

Antihistamine therapy has demonstrated only partial benefits in preventing exercise-induced anaphylaxis and should not be relied on to prevent a severe attack [53]. In one case report, cromolyn completely blocked symptoms and histamine release after wheat ingestion and exercise [72]. Katsunuma et al prevented attacks in a patient with wheat-dependent exercise-induced anaphylaxis by administering sodium bicarbonate just before exercising [64]. They postulated that preventing the acidic pH induced by exercise could inhibit mast cell degranulation.

Long-term follow-up of patients with exercise-induced anaphylaxis shows that most patients have a stabilization (46%) or decrease (47%) in their symptoms over time [49]. Whether patients can achieve a sustained resolution of their symptoms and the ability to return to full exercise is uncertain.

Solar urticaria

Solar urticaria involves the induction of urticaria on direct exposure of the skin to sunlight. It first was described by Merklen in 1904 [73]. The number of patients affected by this condition is small, and most knowledge has been obtained through case reports and a few case series involving small numbers of patients.

Epidemiology

Champion performed a retrospective review of 2310 cases of urticaria seen in his practice over 3 decades and found that only 0.4% were classified as solar urticaria [74]. Humphreys and Hunter did a similar review of 390 patients and found a prevalence of solar urticaria of only 0.5% [75]. There seems to be a higher incidence in women [76]. A case series of 25 patients by Ryckaert and Roelandts in 1998 demonstrated that the mean age at initial presentation to a physician was 35 years (range, 17–71 years) [77]. Symptom onset, however, occurred several years earlier, ranging from 4 to 11 years before presentation.

Many of the potential risk factors for solar urticaria, such as patient age, atopic history, and the wavelength of light responsible for the reaction, seem to vary significantly among the case reports. Whether geographic or racial differences affect the expression of this condition remains to be determined.

Clinical features

Solar urticaria generally is brought to a physician's attention because of the typical appearance of classic wheals. Some episodes present with only erythema, itching, or a sensation of burning. Although these symptoms easily could be

mistaken for a common sunburn, the presentation of solar urticaria is typically more rapid, and symptoms occur only minutes after direct sun exposure. A more delayed onset of symptoms (several hours after light exposure) has been reported in a single patient [78].

Urticaria caused by sun exposure is no different in appearance than urticarias of other causes. The key finding that should arouse suspicion of solar urticaria is the limitation of physical findings to areas of the body exposed to direct sunlight. Thin clothing may allow enough light to pass to induce an urticarial reaction, however. The severity of the symptoms generally increases with the intensity of the sun exposure. Limited exposures provoke only itching or burning erythema, and more prolonged exposure leads to typical wheals. Areas of skin that frequently are exposed to sunlight are less sensitive than areas that more commonly are covered [79]. A more severe reaction may be provoked by purposeful sunbathing rather than by normal daily sunlight exposure. Systemic, anaphylactic reactions are possible if the exposed body surface area is large enough [80].

When the patient is removed from the sun exposure, symptoms usually fade rapidly. Most patients note disappearance of the urticaria within 24 hours. Hives of longer duration can be an important clinical point, as the primary differential diagnosis is polymorphous light eruption. In this condition, skin lesions also appear on sun-exposed areas but have less of a predilection for the face and tend to last 2 to 6 days. The other condition that may present that is similar to solar urticaria is erythropoietic protoporphyria [81]. Although this condition can demonstrate urticaria on sun-exposed areas, the lesions are typically painful rather than itching. Erythropoietic protoporphyria usually presents in early childhood, and there is a family history of the disorder. If differentiation cannot be made on clinical grounds alone, elevated protoporphyrin levels in the blood clarify the diagnosis.

Pathogenesis

It has been hypothesized that solar urticaria is dependent on the presence in the skin of a precursor molecule that is activated by exposure to a particular wavelength of light and becomes a photoallergen. This antigen can be activated in vivo or in vitro by irradiating a sample of the patient's serum [76]. The origin of the precursor molecule has not been determined yet.

There seems to be variability in the possible underlying mechanisms surrounding this putative photoallergen. Leenutphong et al have proposed two types of solar urticaria based on mechanism of action [82]. Patients with type I are believed to manufacture an abnormal precursor molecule that is not found in healthy individuals. Patients with type II could possess a common precursor molecule that is found in all individuals. These two groups respond differently during passive transfer experiments, wherein serum is transferred from an affected to an unaffected individual. Transfer of irradiated serum from patients with type I to normal subjects is variable and only produces a positive result if the

abnormal precursor photoallergen is transferred along with the specific IgE. Patients with type II always should produce a positive transfer, because normal subjects already possess the precursor molecule [83].

The fact that passive transfer is not always successful could indicate that there are different photoallergens at work in different patients. In many patients, the responsible antigen seems to be circulating and can be transferred passively in serum. In one study, however, passive transfer experiments required an injection using epidermal tissue eluates, and the patient's reactivity to sunlight could be eliminated by removing the horny layer of the skin [82]. These results suggest a cutaneous rather than a circulating antigen that would not be transferred using serum.

Diagnostic testing

Clinical history alone is usually insufficient to differentiate solar urticaria from other conditions. The diagnosis can be established with certainty using phototesting. The patient's skin is exposed to varying wavelengths using a monochromatic light source, and a threshold dose, which induces erythema or urticaria, is established. This wavelength of light is referred to as the action spectrum. The reaction generally fades quickly after the test is halted. In some patients, this test failed to provoke urticaria, but exposure to other light sources, such as natural sunlight, high-intensity ultraviolet light, or slide-projector light, induced symptoms [77].

A classification of solar urticaria was proposed by Harber et al in 1963. Six patient categories are based primarily on the action spectrum responsible for that patient's reaction [84]. Because some patients fail to react to monochromatic light [77] and others demonstrate an action spectrum that changes over time [85], this classification system may not be useful in categorizing all patients.

During testing, some patients can be shown to exhibit an inhibition spectrum [86]. When applied to the skin during or immediately after the action spectrum, this wavelength of light inhibits the development of the wheal reaction. This wavelength is typically longer than the action spectrum and is not effective when it is applied before the action spectrum [76], making it unlikely to be useful as prophylactic therapy. A small number of patients seems to demonstrate an augmentation spectrum that, when added to the action spectrum, increases the size of the wheals [76].

Treatment

The treatment for solar urticaria is symptomatic. Antihistamines are the drug of choice and can be used orally or topically. These medications are effective in reducing pruritus and wheal formation but may not eliminate the erythema associated with solar urticaria. In most of the initial studies, terfenadine was used, and higher-than-standard doses often were required to affect symptom relief [87].

Whether this finding is true for all antihistamines, including some of the newer agents, remains to be determined. Topical and systemic steroids can be used if antihistamines are insufficient.

It has been demonstrated that skin that frequently is exposed to sunlight becomes more tolerant than does skin that usually is covered [79]. This principle has led to the use of desensitization as a form of therapy. Patients repeatedly are exposed to ultraviolet light sources and experience a reduction in outbreaks, although the desensitized state typically lasts only a few days. The use of psoralen plus ultraviolet A radiation (PUVA) has been shown to induce a more lasting protection [88], although the potential long-term adverse effects of this form of therapy are greater.

Plasmapheresis has been used alone [89,90] and in conjunction with PUVA therapy [91]. This modality has been reported to improve symptoms in the few patients included in these studies. One study failed to demonstrate a lasting benefit with plasmapheresis [92]. The effectiveness of this therapy may depend on the characteristics of the specific photoallergen at work (ie, circulating antigen versus cutaneous antigen).

The long-term outlook for patients with solar urticaria has been uncertain because the small overall number of cases. A review of 87 patients by Beattie et al [93] found that 25% of the 60 subjects who were available for follow-up reported complete resolution of their conditions. An additional 32% reported improvement, whereas 35% were unchanged, and 8% believed that their conditions had worsened. Most of the original case reports indicated that the condition was persistent, and although many patients experienced overall improvement in symptoms, few patients experienced complete resolution.

Aquagenic urticaria

Aquagenic urticaria is classified as urticaria arising from direct skin contact with water. It must be distinguished from aquagenic pruritus and other physical urticarias, particularly cholinergic and cold-induced urticaria. It is a rare condition, and only a small number of affected patients have been described in the literature. It first was described by Shelley and Rawnsley [94], who reported on three cases in 1964.

Epidemiology

Aquagenic urticaria is a rare disorder with fewer than 50 cases reported in the medical literature, mostly in the form of case reports. Women seem to have a slightly higher incidence than men, and in most cases, the age of onset is at or slightly after puberty. Familial occurrences have been reported on several occasions [95–97], and in one report the condition existed across three generations of a single family [95]. A personal or family history of atopy occasionally is reported, but no consistent association seems to exist.

Clinical features

The lesions of aquagenic urticaria are characteristically small, punctuate (1–3 mm), perifollicular wheals that may occur on all parts of the body, although generally not on the palms and soles. In appearance, they are indistinguishable from the wheals of cholinergic urticaria. In aquagenic urticaria, however, wheals appear rapidly after direct contact with any source of water (ie, distilled, tap, or saline). Wheal formation is not influenced by the temperature or pH of the water [98].

Wheals appear rapidly within 20 to 30 minutes; once the water source is removed from the skin, the wheals generally fade within 30 to 60 minutes [4]. Alcohol and other organic solvents applied to the skin do not lead to wheal formation [97,98]; however, they can potentiate the reaction to water, likely by enhancing the permeability of the skin to water [99]. Systemic symptoms are rare but have been reported [96,100]. A refractory period lasting several hours has been demonstrated after an attack [101]. Repeated, short, purposeful exposures to water can lead to exhaustion of the wheal response [98].

Aquagenic urticaria occasionally is associated with other forms of physical urticaria. Case reports exist of patients with aquagenic urticaria and coexisting dermatographism [96,102], cholinergic urticaria [97,101,102], or cold urticaria [103].

The primary differential diagnoses are cholinergic urticaria and aquagenic pruritus. Because the wheals are identical in aquagenic urticaria and cholinergic urticaria, differentiation of these conditions is dependent on clarification of the inciting triggers. Exercise, sweating, heat, and strong emotions produce cholinergic urticaria, whereas aquagenic urticaria requires the skin to be in direct contact with water. Aquagenic pruritus also occurs on skin contact with water but lacks the visible cutaneous manifestations of aquagenic urticaria.

Pathogenesis

Several lines of evidence have helped improve the understanding of aquagenic urticaria, but the pathogenesis still is poorly understood. Shelley and Rawnsley postulated that water interacted with sebum to form a substance capable of acting as a direct mast cell degranulation, resulting in histamine release [94]. This theory seemed to be confirmed by Chalamidas' study, in which patch testing with a patient's sweat produced only erythema, whereas testing with sweat and sebum produced marked urticaria [98]. A study by Sibbald et al demonstrated that complete removal of the stratum corneum layer of the skin, rather than preventing urticaria, seemed to worsen the reaction on contact with water [99]. These authors also demonstrated that pretreatment with organic solvents enhanced wheal formation to water. They concluded that enhancing the ability of water to penetrate the stratum corneum layer of the skin increases the wheal-provoking effects of water in these patients.

Czarnetzki et al believed that water is simply an ''innocent bystander'' in the process of wheal formation [97]. They postulated that an antigen existed at the

epidermal layer of the skin that could be solubilized by water. The antigen would diffuse deeper to the dermal mast cells, where a reaction would be initiated. Tkach described a patient who experienced urticaria after exposure to tap water, snow, and sweat but who did not develop symptoms after exposure to sea water [104]. He postulated that hypotonic water sources could lead to osmotic pressure changes that indirectly would provoke urticaria.

Activation of the cholinergic pathway has been hypothesized to be the mechanism for aquagenic urticaria [99] because of the ability of the acetylcholine antagonist scopolamine to suppress wheal formation when applied to the skin before water exposure. Another study failed to replicate this finding [97] when pretreatment with atropine did not suppress subsequent wheal formation. Methacholine injection testing, often positive in cholinergic urticaria, is negative in aquagenic urticaria [98]. Serum histamine levels are variable from patient to patient, as is the response to pretreatment with oral antihistamines.

The pathogenesis of aquagenic urticaria remains unclear. Given that all of the studies mentioned were performed with small numbers of subjects, there may be variability in the pathogenesis from patient to patient. There also may be different antigens located at different skin layers, or different effector mechanisms may be involved, with the common end result being the clinical picture of aquagenic urticaria.

Diagnostic testing

Given the significant overlap in potential inciting triggers, it is important to rule out other physical urticarias during the work-up of aquagenic urticaria. Testing for cholinergic and cold-induced urticaria may be warranted. The standard test for aquagenic urticaria is the application of a water compress at 35°C to the upper body for 30 minutes. Although water of any temperature can provoke aquagenic urticaria, keeping the compress at room temperature avoids confusion with cold-induced or local heat urticaria. The upper body is chosen as the preferred site, because other areas, such as the extremities, are affected less commonly in aquagenic urticaria.

In some case reports, rinsing specific areas of the body with water or performing direct bath and shower challenges has been attempted. Use of these approaches may be required when localized testing using a small water compress is negative but may increase the risk for systemic symptoms. Certain areas of the skin with a thickened epidermal layer may be less desirable for testing because of a reduced penetration of water.

Treatment

Histamine levels in blood are often elevated in patients during an attack, and pretreatment with antihistamines has been reported to completely control symptoms in some cases [99,105]. In other cases, a more variable response to antihistamine therapy has occurred. In some cases, whealing and itching still

occur but are reduced significantly, whereas in others there is a failure to adequately control symptoms. Barrier methods have been shown to be effective. In one study, the application of petroleum ointment to a patient's skin before water exposure prevented urticaria formation [99].

In cases in which antihistamines failed to provide symptomatic benefit, other measures have been attempted. Parker et al used UVB light treatments twice a week in a child with coexisting aquagenic urticaria, cholinergic urticaria, and dermatographism; definite improvement was noted by 20 weeks [102]. Two reports have documented the benefits of PUVA therapy in isolated cases [106,107]. Fearfield et al reported a case of a patient with HIV infection, hepatitis C virus infection, and aquagenic urticaria [100]. The patient failed therapy with oral antihistamines but responded dramatically to the anabolic steroid stanozolol. The urticaria was resolved completely until the drug was stopped and symptoms recurred.

Vibratory angioedema

Vibratory angioedema refers to the development of pruritus and swelling after the application of a vibratory stimulus to the skin. The condition first was reported by Patterson et al. They described four members of a family with vibration-induced edema that was passed on in an autosomal dominant inheritance pattern [108].

Epidemiology

Reports of vibratory angioedema are rare in the literature. Patterson et al's initial description of four patients within a family was followed by another familial report [109], and the condition was given the name hereditary vibratory angioedema. Other case reports of patients with vibratory angioedema have been sporadic and generally related to the subject's occupation.

Clinical features

After experiencing an appropriate vibratory stimulus, patients generally complain of local pruritus, erythema, and swelling arising within a few minutes. There is a single case report of a patient who experienced a delayed onset of symptoms at 1 to 2 hours [110]. Symptoms peak in severity at 4 to 6 hours and typically resolve by 24 hours. In some episodes, the symptoms may persist for several days. The severity and duration of the symptoms may vary and seem to be proportional to the intensity and duration of the applied vibratory stimulus and to the area of exposed body surface. Patterson et al's initial report described systemic symptoms of headache and generalized erythema [108]. One patient developed carpal tunnel syndrome, and slowed median nerve conduction was documented only during episodes of edema [111].

Several triggers have been described in vibratory angioedema. Riding a motorcycle, horse, or mountain bike; handling a jackhammer; mowing the lawn; toweling; massaging; clapping; and walking have been reported to provoke symptoms. Occupations that have led to recurring episodes have been machinist [112], carpenter [112], and metal grinder [111]. A secretary who developed symptoms subsequently was diagnosed with a bladder yeast infection [113]. The angioedema completely resolved after prolonged antifungal therapy.

Pathogenesis

The pathogenesis of vibratory angioedema has not been satisfactorily elucidated yet. Elevated levels of serum histamine and mast cell degranulation have been documented during symptomatic episodes [110,112,114], but passive transfer experiments have been negative [108,114]. Most investigators favor a nonimmunologic immediate hypersensitivity reaction. Direct mast cell stimulation from the vibration may lead to degranulation and local release of histamine.

Diagnostic testing

Several methods for reproducing the vibratory stimulus and classifying the reaction have been used in the literature. Guidelines recommend a slight modification of Patterson et al's initial technique [4]. The subject's arm is held on a level plane, and a vortex mixer is placed in contact with the skin. The vibratory stimulus is applied for 5 minutes, and the site is observed for 5 to 6 hours. If the test is positive, the site should develop pruritic erythema and edema around the full circumference of the arm. Dermatographism and pressure urticaria should be excluded using the appropriate tests.

Treatment

Patient avoidance of specific vibratory stimuli is the first line of therapy but, especially with occupational triggers, may not be adequate in all cases. H_1 antihistamines seem to be of value. Lawlor et al reported that terfenadine taken before a vibratory stimulus delayed symptom onset and reduced the overall severity of the attack [115].

Ting et al induced a state of tolerance in a patient by using twice-daily vibration challenges until symptoms were delayed in onset and reduced in duration [114]. The patient eventually achieved complete control of her symptoms by using a 5-minute desensitization protocol every 5 to 7 days. Other authors failed to induce a state of tolerance in their subject [115].

Summary

The physical urticarias reviewed in this article seem to represent a heightened sensitivity by the mast cell to environmental stimuli. The full pathogenesis for

these disorders remains unclear, and future research is needed to elucidate their underlying mechanisms.

Although most of these conditions share the features of rapid onset and relatively short duration, there is enough variability in presentation to occasionally present a diagnostic dilemma. Using the diagnostic techniques described in this article can allow the physician to make a firm diagnosis. Because of the occasional overlap of the triggers and the occasional coexistence of multiple physical urticarias, diagnostic testing should be completed for several of these conditions in each patient. This approach allows the physician to confirm the true diagnosis and definitively exclude others.

Treatment is generally avoidance of known triggers and use of antihistamines for prophylaxis. Other modalities are occasionally effective. Life-threatening, systemic symptoms are rare (except in exercise-induced anaphylaxis) but must be considered. Self-injectable epinephrine should be provided to any patient at risk.

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