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Chronic Inducible Urticaria: Part II

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Abstract

Physical urticaria (PU) is a subgroup of acquired, chronic inducible urticaria which is associated with a known physical trigger. In PU, the symptoms are induced by exogenous physical triggers, such as friction, pressure, vibration, cold, heat, or solar radiation. All the PUs may manifest with both wheals and angioedema at the sites of the triggers with the exceptions that urticaria factitia (UF) (symptomatic dermatographism) presents with wheals only and pressure urticaria presents with angioedema only. More than one form of physically induced urticarias can be present in one patient.

Keywords: physical urticaria, dermatographism, cold urticaria, heat urticaria, solar urticaria

1. Introduction: physical urticarias

Physically induced urticarias are symptomatic dermatographism, cold contact urticaria, heat contact urticaria, solar urticaria, delayed pressure urticaria, and vibratory urticaria. More than one of these can be present in a single patient making it difficult to manage. A known and repeatable physical trigger is the causative agent in these entities.

2. Urticaria factitia (dermatographism)

Urticaria factitia (UF) is also known as dermatographic urticaria and symptomatic dermatographism. UF is the most common type of physical urticaria (PU) [1]. It must be differentiated from simple dermatographism in which whealing without itching is seen after moderate stroking of the skin [2]. White dermatographism which is seen in atopic patients is not related

to UF [3]. UF is commonly seen in young adults and the mean duration of the disease was reported 3–9 years in different studies. The etiology of UF is still unknown [4]. Infections (hepatitis, upper respiratory tract infections), medications (progesterone, statins), and diabetes mellitus have been accused, but still, there is less evidence [5]. The pathogenic mechanism is believed to be the release of histamine following a mechano-immunological trigger [6].

In UF, itchy, white/pink/red wheals are observed after friction, scratching, rubbing, or tight clothing. Wheals appear in a few minutes following the trigger and may last a few hours. UF should come to mind in such cases, and the diagnosis should be made after positive skin provocation test [7].

The provocation in UF can be done by scratching or rubbing the skin with a blunt object (e.g., closed ballpoint pen tip or wooden tongue depressor). The flexor aspect of the forearm is the most suitable site for the provocation. Five to ten minutes of waiting time is mostly enough to conclude [8]. Recent guidelines suggest threshold testing with more advanced devices called the dermatographometer. With this device, predefined and reproducible pressures can be applied to the testing area. The minimal force which is necessary to induce whealing can be determined with dermatographometer and the disease activity in time (i.e., the patient's response to therapy) can be easily monitored. A positive response is noted when the patient shows a wheal response and complain pruritus [9].

Treatment of UF is mostly symptomatic. Avoidance is the best strategy. It is possible to prevent or minimize whealing by some precautions. Decreasing mechanical irritation in daily life is the essential of the therapy [10]. For symptomatic cases, new generation, nonsedating antihistamines are suggested as first-line treatment. In case of failure, the dose can be increased to fourfold. Type of the antihistamine can be changed, leukotriene antagonists and/or H₂ antihistamines can be added [11]. Next two drugs in the treatment course are cyclosporine A and omalizumab [10, 12].

3. Delayed pressure urticaria (DPU)

Delayed pressure urticaria (DPU) manifests with pink/red whealing or angioedema of the skin at sites of sustained pressure, such as tight clothing, walking, or sitting down. It is called delayed because hours (6–8 h) are necessary for it to manifest [9, 13]. The patients suffer from severe pain and burning sensation in contrast to other PUs. Fatigue and arthralgia can accompany. The quality of life is much more affected in DPU patients when compared with other forms of PU. Sometimes, the lesions can last up to 72 h [14].

The diversity of symptoms suggests that other mediators such as cytokines and interleukins play a role in addition to histamine in the pathogenesis of DPU. There is evidence that IL-1, IL-3, IL-6, and tumor necrosis factor alpha (TNF- α) play a role in the etiopathogenesis [12]. More recently, neuropeptides, such as substance P and calcitonin gene-related peptide, have also shown to be taking a part in the formation of DPU [15].

After taking proper history of the patient, if there is a suspicion of DPU, skin provocation test should be performed. Either weighted rods (7 kg weight with a 3 cm wide strap over the shoulder) or dermatographometer can be used for this purpose. Weighted rods should be applied for 15 min and the dermatographometer for 70 sec. If a red-colored edema appears after 6 h of the trigger, the test result is accepted as positive [16].

The etiology of DPU is not clear, so symptomatic treatment and avoidance are the mainstay of the therapy. Angioedema can be made less frequent or less severe with H1 antihistamines [3]. Most of the time, additional efforts are necessary to control the attacks. Leukotriene antagonists, dapsone, sulfasalazine, or combinations of these have been reported to be successfully used in the literature. Systemic steroids can be used in flare-ups. Recent studies show the benefit of omalizumab, but further controlled studies are necessary [17]. Anecdotal reports have shown the efficacy of intravenous immunoglobulins, tranexamic acid, and chloroquine [18, 19]. More recently, good results with gluten-free diet have been reported [14]. Cassano et al. reported remission of DPU after eradication of *Blastocystis hominis* surprisingly [13].

4. Heat contact urticaria (HCU)

Heat contact urticaria (HCU) is a rare type of PU in which wheals appear after contact to objects with temperature higher than the skin temperature itself [20]. The lesions emerge within a few minutes after the trigger and last for a few hours. Most of the patients are 20–45-year-old females. Most of the patients with HU have additional systemic symptoms such as weakness, headache, flushing, diarrhea, shortness of breath, and, even sometimes, syncope [21–23]. Some familial cases with autosomal dominant inheritance have been shown [2]. Most of the time, the trigger is a warm bath. Hot air, heating pads, open fire, heated stove, hair dryers, and indirect sunlight can also cause HU [24].

In case of a suspicion, container filled with hot water should be applied for about 5 min to the skin, or the patient should be asked to shower with hot water at a temperature of 45°C. If the testing area shows a palpable and clearly visible wheal and flare, it is accepted as a positive test. In most of the cases, a burning sensation can accompany the itching. In patients with a positive test result, stimulation time and temperature threshold levels should be measured [25].

Generalized HU must be differentiated from cholinergic urticaria. In HU, the whealing and flares are limited to the contact areas. The lesions are mostly in similar size and morphology. On the contrary, cholinergic urticaria is caused by an increase in the body core temperature and the lesions are small pinpoint hives with flushing [26].

In HCU, the principal of the treatment is to avoid heat if possible. Sometimes, heat desensitization can be effective. For symptomatic cases, H1 antihistamines are the first-line treatment, and in case of failure, the dose can be increased up to fourfold [26]. Omalizumab, montelukast, and cyclosporine are the third-line treatments [27]. Systemic steroids, colchicine, and disodium cromoglycate can be used in resistant cases [8].

5. Cold contact urticaria (CCU)

Cold contact urticaria (CCU) is characterized by the appearance of wheals and angioedema after exposure to cold. Lesions occur a few minutes following the cold contact. Lesions usually do not spread beyond the contact area [28]. This form of PU can be fatal in some cases. After extensive cold contact, severe angioedema or shock can be seen, mostly following swimming in cold water [29]. CCU is mostly seen in young adults and can continue for 5–8 years [2].

There are some rare variants of CCU. In some cases, CCU lesions develop 24–48 h after cold exposure. In this case, it is called *delayed CCU*. In *cold-dependent dermatographism*, the lesions are seen in cold-exposed and mechanically stimulated areas. *Cold-induced cholinergic urticaria* is the case that happens after physical exercise in cold air [30]. Familial cold auto-inflammatory syndrome (FCAS) is a rare autosomal dominant condition in which wheals appear within 2 h of systemic cold exposure. The lesions in this syndrome cannot be brought out by localized cold exposure. In FCAS, CIAS1/NLRP3 mutation leads to the activation of NLRP3 inflammasome complex, and finally, interleukin-1 β is released from the mast cells. That is why FCAS responds dramatically to interleukin-1 antagonists [31].

CCU lesions and symptoms arise as a result of the release of some mediators such as histamine, prostaglandin D₂, platelet-activating factor, and leukotrienes. Yet, it is not known why cold exposure causes the release of these mediators [32]. Half of the CCU patients are positive for antibodies against immunoglobulin E (IgE). IgE binding of some possible, unproven cold-dependent skin antigens can be the reason of mast cell degradation [33]. It is also shown that CCU patients have circulating histamine-releasing factors and positive autologous serum skin test (ASST) [34].

Suspecting CCU or angioedema, one should perform cold stimulation test since fatality has been reported in several cases. In this test, the volar aspect of the forearm is exposed to ice cube in a thin plastic bag for 5 min. Ten minutes after the removal of the bag, the response should be assessed. If a well-demarcated, palpable wheal with a pruritic and burning sensation is present, the test is considered as positive. Ice cube should be in a thin bag in order to avoid any confusion with aquagenic urticaria [35]. Further critical temperature threshold tests with sophisticated devices can enable the patients to avoid situations that cause whealing [28]. More accurate testing is possible with computer-aided thermoelectric Peltier device. This device can also be used for the evaluation of the success of the treatments. In most of the studies, the critical temperature threshold is about 15–20°C [36]. The avoidance of below threshold temperatures is hard to manage in daily life. Even so, the patients should be warned to avoid contact with subthreshold temperatures.

The essential of the treatment of CCU is to avoid cold exposure. Non-sedating H₁ antihistamines are accepted as the first-line therapy by the current European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guidelines [5]. Usually high doses of H₁ antihistamines are necessary to control CCU. Siebenhaar et al. claimed that high dose of desloratadine is better in controlling CCU when compared with

the standard dose [37]. Likewise, Magerl et al. reported that H1 antihistamine up-dosing increases the success rate in the treatment of CCU [38].

In case of failure of therapy with H1 antihistamines, there is lack of well-studied alternative treatment options. Boyce JA reported successful treatment of cold-induced urticaria/anaphylaxis with omalizumab (anti-IgE) [39]. In 2011, Gualdi et al. claimed that a patient who had CCU healed with the use of etanercept for the treatment of co-existing psoriasis vulgaris. It was the first case report regarding the efficacy of etanercept in CCU [40]. Interleukin-1 receptor antagonist (anakinra) was shown to be effective in controlling severe idiopathic cold urticaria [41]. But more controlled studies are necessary to show the effects of omalizumab, etanercept, and anakinra in CCU.

Cold tolerance induction and maintenance therapy can also be tried with precaution due to the risk of anaphylaxis. In this procedure, the patient starts daily showers, first with water temperatures above the threshold and in time, the temperature of the water is decreased gradually. Acquired tolerance is maintained with daily cold showers for a long time [42].

6. Vibratory urticaria (VU)

Vibratory urticaria (VU) is a rare form of PU in which whealing and pruritus of the skin is observed after vibration at the contact area [43]. For proper diagnosis, provocation testing can be done by using a laboratory vortex mixer at a frequency of 1000 r.p.m. Test is considered positive with swelling 10 min after provocation [4]. Nonsedating H1 antihistamines are the first-line therapy [9].

7. Solar urticaria (SU)

Solar urticaria (SU) is characterized by wheals and sometimes angioedema after visible or ultraviolet (UV) light exposure [44]. Young adults are more commonly affected with a female predominance. The lesions which develop within 10 min of solar exposure are limited to the exposed areas. There are some variants of SU. Monfrecola et al. reported a case of solar urticaria with delayed onset [45]. Torinuki reported two cases with solar urticaria manifesting pruritic erythema but no whealing [46].

It is thought that some unknown photo-allergens that are produced in the skin after sun exposure cross-react with IgE on mast cells, and as a result, histamine and other inflammatory mediators are released. Norris et al. and Esdaile et al. claimed that bruised skin is more prone to the formation of SU. They tried to explain this by the migration of photo-allergens into the skin through damaged vessels [47, 48].

In a chronic urticaria patient, after history taking, if there is a suspicion of SU, we should perform provocation test. For this purpose, solar simulators can be used. Provocation should be performed on body areas which are usually not exposed to sunlight, such as the buttocks, and

UVA, UVB, and visible light should be used separately. In a positive test result which means flare and whealing within 10 min of the exposure, threshold testing should also be done using increasing radiation doses [8].

It is difficult to manage SU. Avoidance of the sunlight exposure is almost impossible. According to the guidelines, H1 antihistamines are the first-line treatment options. But only one-third of the patients respond well to the antihistamines. Repeated sunlight exposure can induce tolerance [45]. For this purpose, PUVA and narrow-band UVB can be used. Güzelbey et al. reported successful treatment of SU with anti-immunoglobulin E therapy [49]. There are few other studies in the literature showing the efficacy or inefficacy of omalizumab [50, 51].

Hughes et al. and Correia et al. reported that SU can be successfully treated with intravenous immunoglobulin [52, 53]. On the contrary, Llamas-Velasco et al. claimed that intravenous immunoglobulin was ineffective in the treatment of SU [54]. In 2011, Haylett et al. revealed that systemic photoprotection was possible with alpha-melanocyte-stimulating hormone (afamelanotide). Its mechanism of action is to increase melanization of the skin. With this effect, it protects the skin from the penetration of UV and visible wavelengths [55].

8. Conclusion

Physically induced urticarias are hard to manage. Avoidance is the best treatment option, but it is impossible most of the time. We should be alert that more than one form can be together in a patient. Although antihistamines are the first-line therapy, usually other options are required to manage.

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