ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Provocation tests for chronic inducible urticaria: the experience of a urticaria center of reference and excellence

Testes de provocação para urticárias crônicas induzidas: a experiência de um centro de referência e excelência em urticária - UCARE

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ABSTRACT

Introduction: Urticaria is determined by mast cell activation that presents as wheals, angioedema, or both. Urticaria is classified according to its duration into two forms: acute (< 6 weeks) and chronic (> 6 weeks). Chronic urticaria includes chronic spontaneous urticaria and chronic inducible urticaria. Chronic inducible urticarias include dermographism, delayed pressure urticaria, cold, heat, solar, aquagenic, cholinergic, and vibratory urticaria/angioedema. Chronic inducible urticaria can be diagnosed through clinical history, physical examination, and the reproduction of lesions through provocation tests. **Objective:** To describe the profile of positive provocation tests for chronic inducible urticaria performed at an urticaria center of reference and excellence (GA^{2}LEN UCARE). **Methods:** We retrospectively evaluated the results of provocation tests performed between December 2017 and September 2021 in 114 patients with a history suggestive of one or more types of chronic inducible urticaria. **Results:** The sample included 88 (77%) female and 26 (23%) male patients. The following were diagnosed through positive provocation tests: 65 cases of dermographism (FricTest® and/or dermographometer); 23 cases of delayed pressure urticaria (all diagnosed with a dermographometer and 11 confirmed with the Warin test); 11 cases of cold urticaria (temperatures ≤ 27°C) and 3 cases of heat urticaria (temperatures ≥ 38°C), all diagnosed with TempTest® 4.0; 4 cases of cholinergic urticaria, all diagnosed with the Modified Test for Cholinergic Urticaria-HUCFF-UFRJ, and 1 case of vibratory urticaria. No patient tested positive for solar or aquagenic urticaria. Seven patients have been negative. **Conclusion:** Provocation tests, which use direct and safe stimuli as triggers, allow physicians and patients to confirm the disease's causative stimulus and its thresholds.

Keywords: Chronic urticaria, urticaria, angioedema, allergy and immunology.

RESUMO

Introdução: A urticária é determinada pela ativação de mastócitos que se apresenta por urticas, angioedema ou ambos. A urticária é classificada de acordo quanto a sua duração, em duas formas: aguda (UA < 6 semanas) e crônica (UC > 6 semanas). A UC compreende Urticária Crônica Espontânea (UCE) e Urticárias Crônicas Induzidas (UCInd). Entre as UCInd estão o dermografismo, urticária por pressão tardia (UPT), frio, calor, solar, aquagênica, colinérgica e urticária/angioedema vibratório. As UCInd podem ser diagnosticadas por meio da história clínica, exame físico e da reprodução das lesões através dos testes de provocação. **Objetivo:** Descrever o perfil dos testes de provocação positivos para UCInd realizados em um Centro de Referência e Excelência em Urticária (GA^{2}LEN UCARE). **Métodos:** Foram avaliados, retrospectivamente, os resultados dos testes de provocação para UCInd, realizados de dezembro de 2017 a setembro de 2021, de 114 pacientes que apresentavam história sugestiva de uma ou mais UCInd. **Resultados:** Dos 114 pacientes avaliados, oitenta e oito (77%) eram do sexo feminino e 26 (23%) do masculino. Foram diagnosticados, através de testes de provocação positivos: 65 dermografismos (FricTest® e/ou dermografômetro); 23 UPT (23 diagnosticados com o uso do dermografômetro e 11 também confirmados através do teste de Warin); 11 urticárias ao frio (temperaturas iguais ou inferiores a 27 °C) e 3 urticárias ao calor (temperaturas iguais ou superiores a 38 °C), todos diagnosticados com o TempTest® versão 4.0; 4 urticárias colinérgicas, diagnosticados através do Teste Modificado para Urticária Colinérgica - HUCFF-UFRJ e 1 urticária vibratória. Nenhum paciente apresentou teste positivo para urticária solar ou aquagênica. Sete pacientes foram negativos. **Conclusão:** Os testes de provocação, através do estímulo direto e seguro com o desencadeante, permitem ao médico avaliador e ao paciente a compreensão e a confirmação do estímulo causador da enfermidade em questão e seus limiares.

Descritores: Urticária crônica, urticária, angioedema, alergia e imunologia.

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Introduction

Urticaria is a disease determined by mast cell activation and presents with wheals, angioedema, or both.[1] Urticaria is classified according to its duration into two forms: acute (AU) and chronic (CU). CU is characterized by persistence of symptoms for 6 weeks or more. CU comprises chronic spontaneous urticaria (CSU) and chronic inducible urticarias (CIndU), which include physical and nonphysical urticarias.[1-3]

CIndU are defined as a group of diseases characterized by wheals and/or angioedema induced by external stimuli, including dermographism, delayed pressure urticaria (DPU), cold urticaria, heat urticaria, solar urticaria, aquagenic urticaria, cholinergic urticaria, and vibratory urticaria/angioedema.[2,3]

The prevalence of physical urticarias (PU) ranges from 20% to 30% of the cases of urticaria in adults, and from 6.2 to 25.5% in children. PU are estimated to be present in up to 5% of the general population; additionally, they are present in 10 to 50% of patients with CU, with symptomatic dermographism and DPU being the most common in our setting.[4] Patients with both CSU and PU usually show worse prognosis and longer duration of these diseases.[5,6]

CIndU may be diagnosed through clinical history, physician examination, and the reproduction of lesions through provocation tests.[7]

Dermographism is the most frequent CIndU among the general population (2-5%) and are responsible for 30-50% of cases of PU.[2] This type of PU is characterized by the occurrence of wheals after local pressure or shearing force on the skin, manifesting especially after scratching or rubbing, with the development of local itchy lesions.[8,9]

Some instruments, such dermographometer, calibrated at pressures from 20 to 160 g/mm^2 (196-1569 kPa), and Fric Test® (Moxie, Berlin, Germany), a plastic device with four pins measuring 3.0, 3.5, 4.0 and 4.5 mm in length, respectively, were developed to test dermographism and determine the symptomatic threshold. In addition to these instruments, blunt and smooth objects, such as a closed ballpoint pen tip or a spatula, may be rubbed on the volar surface of the forearm or superior surface of the back.[10]

Studies describe a low prevalence of DPU, which occurs in less than 5% of cases of CIndU.[11] Patients with DPU develop wheals and/or angioedema 4 to 6 hours after the skin is exposed to sustained pressure stimulation. Lesions may appear up to 12-24 hours and may last up to 72 hours.[12,13] The reaction is not usually associated with itching, but may be accompanied by pain and/or burning. It is essential to differentiate symptomatic dermographism from DPU, and time of appearance of lesions is one of the characteristics that differentiate these CIndU. Another characteristic is that DPU presents with painful and non-itchy lesions. It is worth highlighting that these forms may be associated.[14,15]

Provocation tests to assess DPU aim to simulate pressure to the skin during a given sustained time, to then evaluate the skin reaction at stipulated time points. Test methods include the suspension of weights over the shoulder, the application of rods, lowered vertically onto the skin and supported in a frame, on the back, thigh, or forearm, or the use of a dermographometer.[7]

Cold urticaria is defined by the appearance of wheals after exposure to cold, either by solid objects, air, or cold liquids. These lesions are caused by the release of histamine, leukotrienes, and other pro-inflammatory mediators from mast cells.[2,5,16] According to some authors, cold urticaria is the second most common type of physical inducible urticaria. Its annual incidence is estimated at 0.05%, its frequency ranges from 5 to 30%, with a predominance in the female sex (2:1), and the most affected age group is 20 to 30 years old.[2,17,18]

Lesions are usually limited to the site of contact with cold (wheals and angioedema), but they can be generalized and accompanied by systemic manifestations, including progression to acute respiratory failure and anaphylaxis. These mainly occur in situations such as carrying refrigerated objects, swimming in ice water, staying, or entering a refrigerated environment.[19]

Challenge methods for cold urticaria include the classic "ice cube test" and the TempTest®.[7]

Heat urticaria is a rare form of CIndU characterized by wheals appearing soon after exposure to heat. Due to its rareness, there are no robust data on its prevalence. Most cases occur in women (82%). The mean age of onset of heat urticaria is 34.4 ± 19.5 years, ranging from 4 to 78 years.[20]

It may occur in two forms: localized and generalized, depending on whether the reaction is limited to the directly exposed portion of the skin or affects distant sites, respectively.[21]

Wheals appear 2-15 minutes after exposure and may last for approximately 1-3 hours. A burning sensation on the site of the lesion may also occur.

Some patients may present systemic manifestations such as syncope, fatigue, nausea, vomiting, abdominal pain, fever, and dyspnea. These manifestations occur especially if extensive areas are involved. Challenge methods for heat urticaria include the classic "ice cube test" and TempTest®.[7,22]

Patients with solar urticaria develop wheals shortly after exposure of skin to sunlight (UVA, 320-400 nm; or visible wavelengths, 400-600 nm). Less frequently, lesions are induced by UVB (280-320 nm) or infrared radiation (> 600 nm). Solar urticaria accounts for 7% of all photodermatoses. The prevalence of this CIndU ranges from 0.4–0.5% of patients with CUs.[7,23,24]

Solar urticaria is classified into two types: type I occurs in patients who have precursors located in the serum, plasma or cutaneous tissue fluid that become photoallergens once activated by the appropriate wavelength and bind to IgE receptors, resulting in degranulation of mast cells and other inflammatory mediators. Type II is also IgE-mediated, but precursors are found in both healthy individuals and patients with solar urticaria.[5,25]

The diagnosis of solar urticaria is made by testing the individual for several wavelengths to simulate provocation of urticaria.[7]

Patients with vibratory urticaria/angioedema present itching and wheals minutes after the skin is exposed to vibratory stimuli, such as riding a motorcycle, riding a horse, practicing mountain bike, using a gyratory crusher or a lawn mower, and playing musical instruments such as the electric guitar. This subtype of urticaria may have a familial etiology, with a dominant autosomal inheritance. Its prevalence is approximately 0.1% of patients with CU. Vibratory urticaria may be tested by standardized challenge with a mixer vortex.[2,7,10]

Aquagenic urticaria is a rare condition resulting from contact with water, regardless of its temperature. Approximately 30 minutes after contact with water, patients develop wheals measuring 1-2 mm. These are mostly isolated cases, although familial cases were reported.[26,27]

Its fisiopatogenia is not well understood; however, there is evidence that water would act as a carrier for an epidermal antigen that is able to activate mast cells.[28,29] Provocation test for aquagenic urticaria consists of using a compress soaked in water at a temperature close to body temperature.[7]

Cholinergic urticaria was first described by Duke in 1924[9] and is characterized by the appearance of micropapular lesions related to an increase in body temperature from physical exercise or local application of heat; in addition to emotional stress, spicy foods, or hot drinks. The lesions are approximately between 1 and 3 mm, located on the trunk and upper limbs.[7,30,31]

Cholinergic urticaria is more common between the second and the third decades of life. Furthermore, its prevalence ranges from 4 to 11% in the general population.[32]

Four subtypes of cholinergic urticaria were proposed, based on its pathogenesis and clinical characteristics: the first type refers to cholinergic urticaria related to sweat allergy and without angioedema, with possible hypersensitivity to sweet after it is released from ducts; the second type is named follicular-type cholinergic urticaria with a positive autologous serum skin test is hypothesized to be caused by mast cell activation through acetylcholine and/or specific antigens located on the epidermis, inducing urticaria around the follicles; the third type consists of cholinergic urticaria with palpebral angioedema; and the fourth type is known as cholinergic urticaria with acquired anhidrosis and/or hypohidrosis.[33]

Lesions tend to last 15 to 60 minutes and may be associated with local angioedema. If cholinergic urticaria is suspected, it is important to differentiate it from exercise-induced anaphylaxis, aquagenic urticaria, adrenergic urticaria, and cold-induced cholinergic urticaria.[33,34]

We have recently reported a case in which the patient underwent challenge test for cholinergic urticaria, using a flight of stairs (13 steps) and parameters similar to a previously described standardized protocol. A frequency meter (Polar F11®) was used to measure and control heart rate (HR). The patient was instructed to go up and down in order to increase his HR by 15 bpm each 5 minutes, being intensified, so as to reach 90 bpm over base HR 30 min later. After 15 min and 45 bpm over baseline, he showed micropapular lesions and erythema on his face, chest, and limbs, and a positive test in mild exercise (57% of HRMax).[35]

CIndU are diseases that visibly impair patient's quality of life, especially due to limitations in environmental exposure, often including the work environment.[36]

Therefore, the aim of this study is to describe the profile of positive provocation tests for CIndU

performed at an Urticaria Center of Reference and Excellence (GA²LEN UCARE).

Methods

We retrospectively evaluated the results of provocation tests for CIndU performed between December 2017 and September 2021 in 114 patients with a history suggestive of one or more types of CIndU.

Results

Of the 114 patients evaluated, 88 (77%) were female and 26 (23%) were male. The following forms of CIndU were diagnosed through positive provocation tests: 65 cases of dermographism (Fric Test® and/or dermographometer); 23 cases of DPU (all diagnosed with a dermographometer and 11 confirmed with the Warin test); 11 cases of cold urticaria (temperatures ≤ 27°C); 3 cases of heat urticaria (temperatures ≥ 38°C), all diagnosed with TempTest® 4.0; 4 cases of cholinergic urticaria, all diagnosed with the Modified Test for Cholinergic Urticaria – HUCFF-UFRJ; and 1 case of vibratory urticaria. No patient tested positive for solar or aquagenic urticaria (Figure 1).

We found associations between different types of CIndU in 17 patients tested in the study period, including 11 associations between dermographism and DPU, 4 between DPU and cold urticaria, 1 between cholinergic and vibratory urticaria, and 1 tripe association between dermographism, DPU, and heat urticaria (Figure 2). Seven patients tested negative.

Discussion

CIndU are diseases that visibly impair patient's quality of life, due to limitations in environmental exposure, often including the work environment.

Our data corroborate findings from other epidemiological studies showing a higher prevalence of CIndU in females (2:1 ratio); however, the female-male prevalence ratio in our sample (4:1) was higher than that of published data.

The prevalence of CIndU is variable, and dermographism (10-50%) and cold urticaria (5-30%) are reported to be the most prevalent, followed by DPU, which accounts for 5% of CIndU. In our sample, the prevalence of dermographism (60%) and DPU (21%) was higher than that previously reported; and cold urticaria showed a similar prevalence, despite being close to the lower threshold (9%).

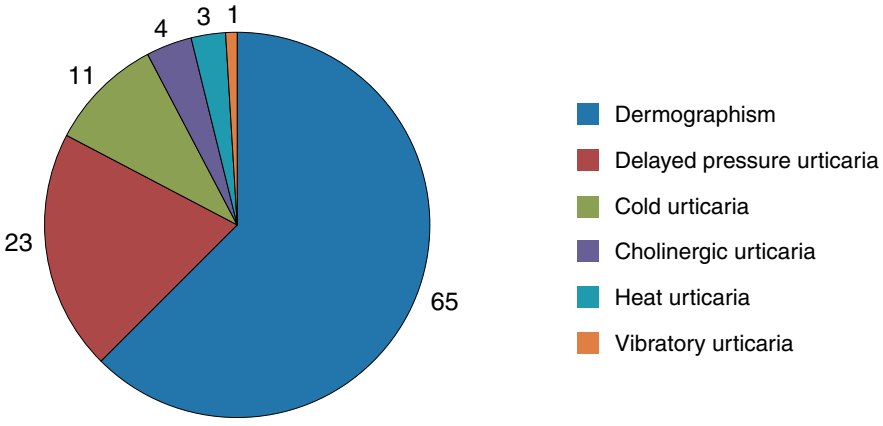

Figure 1
Positive provocation tests

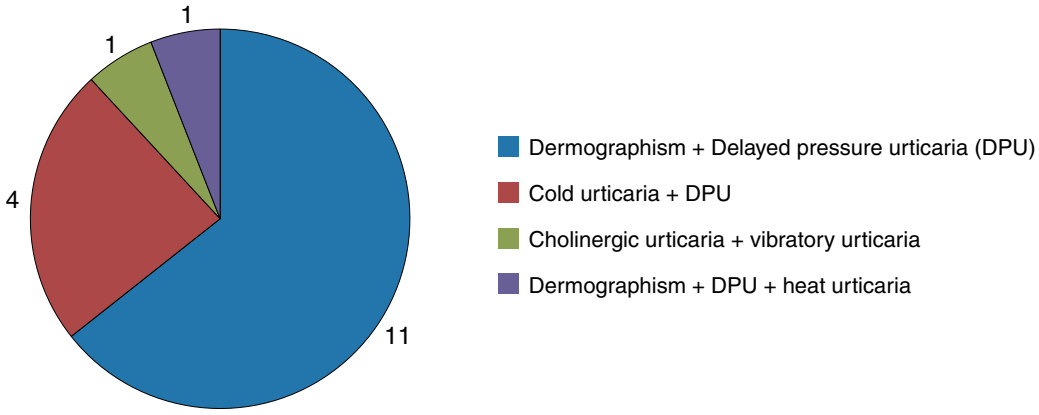

Figure 2
Associations between CIndU diagnosed through specific provocation tests

Data on the prevalence of heat urticaria are rare. In the sample evaluated, we found 3 cases (2.7%) among the 114 testes performed.

With regard to urticarias defined by exposure to temperature variations (cold and heat), we should carefully analyze the reason for these findings, i.e., why cold urticaria presented a prevalence close to the lowest values found in the literature, and heat urticaria showed opposite results. Therefore, the location of Brazil and, specifically, the place of residence of the study population, which has a subtropical climate, is linked to positive natural selection with regard to heat and negative with regard to cold.

Cholinergic urticaria has a prevalence from 4 to 11% in the general population, and was found in 4 individuals (3.5%), a percentage close to that reported in the literature. Once again, climate local conditions are linked to practice of outdoor sports and work activities, a fact that makes the population considerably more exposed to increased body temperature, and thus, to symptoms of this CIndU. However, it is worth investigating the low accurate diagnosis of cholinergic urticaria and referral to specialized care, which is essential in the subsequent management of these cases.

Similar to cholinergic urticaria, tests for vibratory urticaria resulted in only one 1 positive test in the study sample, which is closely consistent with other studies, because this CIndU is rare, with a prevalence < 1%.

It is not common for an individual to present more than one form of CIndU; however, 17 associations between CIndU were observed in our sample, including a patient who presented three forms of CIndU.

These differences in prevalence and associations described between different CIndU should be critically analyzed, since the University Hospital where provocations tests were performed provides tertiary care, and, consequently, has a greater number of referrals to specialized care.

Regarding the divergence between the two methods used to diagnose DPU in our service, a greater accuracy was observed in the use of dermographometer (23) than in the Warin Test (11). We believe that this discrepancy is associated with standardization of the latter method, due to the lack of robust studies, while the first method has accurate calculations aimed at selecting proper pressure for specific stimulus, as previously described.

Conclusion

Provocation tests, which use direct and safe stimuli as triggers, allow physicians and patients to confirm the disease's causative stimulus and its thresholds. Therefore, encouraging the use of available validated methods for diagnosis and proper monitoring of CIndU has an inestimable value for good medical practice.

Additional studies are necessary to assess the prevalence of CIndU in the local population, as well as studies aiming to develop new cost-effective challenge techniques.

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