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REVIEW ARTICLE

Cold-induced urticaria and the risk of anaphylaxis

Urticária ao frio e o seu risco de anafilaxia

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ABSTRACT

Cold urticaria (CU) is characterized by the appearance of papules or angioedema after exposure to cold. It may present with mild to severe symptoms and may even lead to anaphylaxis. The risk of systemic reactions is high. We aim to remember this important pathology and show its strong relationship with anaphylaxis. Cold weather is one of the most common triggers for the onset of symptoms, with variables including humidity and thermal sensation. It is divided into acquired or familiar forms. The diagnosis is made in patients with a suggestive medical history and should be checked with a stimulation test. The central aspect of treatment is to avoid cold stimuli. The prescription of epinephrine autoinjector for groups that are at high risk of systemic reactions is ideal. In conclusion, we warn that health professionals should be aware of CU to recognize the risk of anaphylaxis in these patients.

PALAVRAS-CHAVE
Adrenalina
Anafilaxia Urticária ao frio

RESUMO

A urticária ao frio (UF) é caracterizada pelo aparecimento de pápulas ou angioedema após exposição ao frio, podendo se apresentar com sintomas leves a graves e levar inclusive à anafilaxia. O risco de reações sistêmicas é alto. O clima frio é um dos gatilhos mais comuns para o início dos sintomas, com variáveis que incluem umidade e sensação térmica. A UF é dividida em forma adquirida ou familiar. O diagnóstico é feito em pacientes com história clínica sugestiva e deve ser verificado com teste de estimulação. O principal aspecto do tratamento é evitar estímulos frios. A prescrição de adrenalina auto injetável para grupos que estão em alto risco de reações sistêmicas é o ideal. Os profissionais de saúde devem estar cientes da urticária ao frio para reconhecer o risco de anafilaxia nesses pacientes.

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INTRODUCTION

Cold-induced urticaria (CU) is characterized by the appearance of wheals[1] or angioedema[2] after exposure to cold. It is an uncommon subtype of physical urticaria that can present with mild symptoms (localized reaction) and severe reactions, leading to anaphylaxis[3].

Thus, patients with CU may also be at risk of systemic reactions (e.g., respiratory distress, such as dyspnea or wheezing, or vertigo with hypotension, fainting, disorientation, or shock), especially when large areas of the body are exposed to aquatic activities. Some studies suggest that the rate of systemic reactions is significant[4]. In a retrospective case series, 36.7% of children with CU had a history of systemic symptoms[4,5]. In a prospective study, 25.8% of individuals over 30 years old with CU experienced severe systemic reactions[4,6], and additional studies reported this risk in 40 to 41% of cold-sensitive patients[4,7,8]. Generally, the rate of systemic reactions is high for this population[4].

PATHOPHYSIOLOGY

The pathogenesis of CU is not yet fully understood, but the symptoms are thought to result from mast cell activation, their degranulation, and the subsequent release of histamine and other pro-inflammatory mediators. This results in itching, burning, and erythema due to activation of the cutaneous innervation and vasodilation, with plasma leakage generating wheals and angioedema. As in the case of CU, physically induced wheals do not have a late-phase response after the onset of the condition and, therefore, their lesions do not usually last more than 2 h, while individual lesions in patients with spontaneous chronic urticaria last from 4 to 36 h[9]. In some patients, immunoglobulin E has been shown to be a relevant factor in mast cell activation[10].

CLINICAL CHARACTERISTICS

CU is clinically manifested by the development of wheals (swollen erythematous papules) and/or angioedema after the skin is exposed to cold air, cold liquids, or frozen objects. These lesions typically develop minutes after contact with a cold stimulus and are usually limited to the exposed area. However, extensive cold contact can result in symptoms of generalized urticaria and/or systemic reactions, including headache, dyspnea, hypotension, and loss of consciousness, most often observed during aquatic exposure. Cold weather is one of the most common triggers for the onset of symptoms, with variables including temperature, humidity, and thermal sensation[11].

EPIDEMIOLOGY

CU is the second most common form of physical urticaria. The annual incidence is estimated at 0.05% in the general population. It is more common in young adults, and there is a slight predominance in females[11]. Additionally, within physical urticarias, its frequency varies from 5.2% to 33.8% depending on the study and geographic region, with higher incidences reported in regions with lower temperatures[6]. Studies suggest that patients with CU are more likely to present other types of physical urticaria[7]. A review of medical records verified that 30% had another type of concomitant urticaria, 19% dermographism, and 7% cholinergic urticaria[7]. Other studies have described 32%[12] and 37%[13] of patients with this association. These patients often present with a history of asthma (46.7%), allergic rhinitis (50%) and/or a family history of atopic disease (89.3%)[3].

A review of the medical records of children under 18 with a diagnosis of CU showed that 18.6% had anaphylaxis, and swimming was responsible for 77.6% of these reactions, followed by other causes that included the ingestion of cold food or beverages, or exposure to cold air. The mean age at diagnosis was 8.9 years, with peak incidences at 4 and 15. Overall, boys and girls were diagnosed with equal frequency, though the percentage of anaphylaxis was higher in girls (58.4%). A positive stimulus test result was significantly associated with an increased risk of anaphylaxis; however, it is worth noting that 12% of patients with a negative test result also presented anaphylaxis. Other documented factors were family history of atopy in 73.3% and reports of CU in the family in 5.8%. Association with other urticarias was also observed in the pediatric age group, though this was not associated with an increase in episodes of severe reactions[14]. The results of this review corroborate those of another study6 that suggested that patients with severe systemic reactions have a lower probability of resolving the disease, and this rate of resolution is even lower in children[14].

Cold exposure as the etiology for anaphylaxis in other situations, such as the perioperative period, should be considered.This condition is probably underdiagnosed given many differential diagnoses with similar clinical features, such as allergic reactions to antibiotics and neuromuscular blockers. In a recent case report, severe intraoperative anaphylaxis with hypotension and desaturation was observed, associated with diffuse urticaria and angioedema of the lips, which stabilized after the use of adrenaline. Previous reports of atopy and urticaria with the need for prophylactic antihistamine use in exposure to cold temperatures confirmed the diagnosis and exclusion of other agents as the cause of the severe reaction after allergy tests[15].

CLASSIFICATION

CU is divided into acquired (ACU) and familial forms (FCU). ACU can be primary or secondary[16]. The most common presentation of primary ACU is produced by a cold stimulus with no associated underlying etiology[3].

Secondary ACU shows evidence of an underlying cause or disease associated with the induction of urticaria after a cold stimulus[2]. Association with viral infections, such as hepatitis, mononucleosis, borreliosis and HIV, has been reported, with *Helicobacter pylori*, toxoplasmosis, and other parasitic infections. Upper

respiratory, dental, and urogenital tract infections can be present, explaining the infrequent positive response of these patients to antibiotic therapy[17]. Other conditions that act as initial triggers are medications3 and the presence of serum cryoproteins (cryoglobulins, cryoagglutinins and cryofibrinogen)16. The most common cause of secondary CU is cryoglobulinemia[3]. This entity is a clinical syndrome that results from systemic inflammation caused by immune complexes containing cryoglobulins.However, patients with this disorder present urticaria less frequently than with signs and symptoms of cutaneous (purpura) or systemic vasculitis, kidney disease, or other organic manifestations[18].

In addition to these forms, there are hereditary or familial forms, a rare group of autoimmune diseases called cryopyrin-associated periodic syndrome (CAPS) that leads to mast cell degranulation and urticaria. The 3 disorders that make up this group are familial cold autoinflammatory syndrome (FCAS) or FCU, Muckle-Well syndrome, and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurological, cutaneous, articular syndrome.These disorders are on a range of disease severity, with NOMID representing the most severe form, Muckle-Well syndrome an intermediate form, and FCAS/FCU the mildest phenotype in the group and the disease that shows the best prognosis. These disorders are mutations in the cryopyrin gene inherited from an autosomal dominant gene. Most of these patients will present fever and urticaria and/or angioedema in response to cold stimuli[3].

CU is further divided into typical and atypical forms. The best known is the typical form, characterized by the appearance of wheals in areas stimulated by cold and confirmed by a positive response to the specific stimulation test. In contrast, the atypical form also presents symptoms in areas not directly exposed to the cold and the specific stimulus test is negative. In both forms, hypotension due to generalized exposure to cold is described[1].

DIAGNOSIS

Diagnosis is typically made in patients with a clinical history of urticaria or angioedema after exposure to cold and should be adequately confirmed with specific stimulation testing, such as the ice cube test or determined by the TempTest®[2]. Medical history should provide information on exposure, a type of skin lesion and associated symptoms (fever, joint pain, vomiting, diarrhea, abdominal pain)[3].

The ice cube test, considered a standard test, consists of applying an ice cube wrapped in a plastic bag over the volar region of the forearm for 5 min. A positive result is defined by the formation of a wheal within 10 min of removing the ice cube[3]. The use of a plastic bag avoids direct skin contact with water, ruling out the possibility of aquagenic urticaria[11]. This test shows a sensitivity of 83% and a specificity of 100%[3].

The use of a TempTest® challenge device, which provides a continuous temperature gradient along its length (from 4 to 44°C), allows reproducible and standardized cold challenge tests. It should be performed for 5 min. In some patients, shorter or longer challenge times may be appropriate, for example, 30 s in patients who are sensitive and/or at risk of severe reactions, or up to 20 min in patients with a positive history but no wheals after the standard test[11]. This test shows a sensitivity of 93% and a specificity of 100%[3].

In patients who present with a positive reaction to the stimulus test, it is necessary to perform the threshold test to determine the stimulation time limit and/or temperature limit. The stimulation time threshold is the shortest duration of exposure to cold that induces a positive reaction, varying the application time required for a cutaneous response of a wheal or hyperemia. It can be performed using an ice cube or the TempTest®. Ice cube stimulation time thresholds less than or equal to 3 min are associated with higher disease activity. The temperature threshold, i.e., the highest temperature sufficient to induce a positive test result, must be determined whenever a TempTest® is available. Defining temperature thresholds enables patients to avoid risky situations. These measures are useful for assessing disease severity, disease activity, and therapeutic efficacy[11].

Alternative testing methods may be required in patients with a negative ice cube test, for example, immersing an arm in cold water at 5 to 10°C for 10 min. The test response must be evaluated 10 min after the provocation test and is considered positive when a wheal or hyperemia presents at the site, accompanied by itching and/or burning sensations in most cases[11].

Laboratory tests should be considered to discard differential diagnoses, such as serum cryoglobulins and/or cold agglutinins, C-reactive protein, erythrocyte sedimentation rate, amyloid A, biopsy, and genetic testing. Other exams can be added using the patient's medical and clinical status as a guide[3].

TREATMENT

The main feature of the treatment is avoidance. Patients should avoid cold stimuli, including cold foods, cold liquids, cold air, or swimming in cold water. When cold air is a stimulus, patients should be instructed to dress appropriately and maintain a warmer body temperature. Those who have presented anaphylactic reactions and where it is important to participate in certain activities, such as swimming, must have ready access to self-injecting epinephrine[3]. In specific situations, such as an intraoperative period, avoiding exposure to cold during surgical procedures is recommended to manage these patients successfully. Attention to the temperature of the environment, the use of heating blankets, corticosteroids, and antihistamines in the preoperative period, among other medications, also prevent this condition[14].

First-line symptomatic treatment is the use of non-sedating H1 antihistamines11, known as second-generation antihistamines, such as cetirizine[3,19-21], loratadine[3,20], desloratadine[3,19,22,23], bilastine[19,24], and rupatadine[19,25,26]. A review published in 2020 examined the effectiveness of antihistamines in previous studies. The benefits of treatment were reported in all

studies regarding the rate of responders, clinical improvement, and improvement in specific stimulus tests. Bilastine, desloratadine and rupatadine led to complete response and significant reductions in itching and reaction to the stimulus test, while higher doses showed a significant increase in efficiency compared with the standard dose[19].

A standard dose of these medications does not provide complete protection in many patients, even when used daily. Thus, high doses of anti-H1 antihistamines, up to 4 times the standard dose, are more effective in CU and should be tried in patients who do not respond to the initial dose[11].

Brazilian review articles also indicate prescribing classic antihistamines, such as hydroxyzine and cyproheptadine[15]. In the past, cyproheptadine and ketotifen have been commonly used to treat CU[27]; however, these drugs are not considered better than most modern drugs for treating CU and have adverse effects common to other first-generation antihistamines (e.g., sedation and anticholinergic effects)[15].

An H2 antihistamine (e.g., ranitidine) can be combined with an H1 antihistamine for a synergistic effect for refractory cases[3,28]. These are reversible and competitive histamine H2 receptor blockers that block vasodilation and probably lead to less edema formation in urticaria. The combination of H1 and H2 antagonists can be helpful to control itching and hyperemia.

The effects of treatment with antibiotics[11], such as doxycycline[29], can be beneficial for patients with CU even with complete remission of symptoms, as shown by several case reports[30-34]. A retrospective analysis using 200 mg/day of doxycycline for 7 to 28 days showed complete remission in 19% of patients and partial remission in 15% after treatment.Response assessment before and after antibiotic therapy was conducted after the discontinuation of antihistamines for at least 48 h. This response was not associated with disease duration or severity, patient age, or treatment period[29]. Other antibiotics reported to relieve symptoms and induce complete remission in some patients following treatment were penicillin for 2 to four weeks and tetracyclines for 2 weeks[33,34]. The effects of this class can be explained by their role in the underlying chronic subclinical bacterial infections that cause and maintain CU. Another factor that explains this benefit is immunoregulation through its impact on cytokine production. Tetracyclines, and particularly doxycycline, suppress tumor necrosis factor-alpha (TNF-α) and interleukins IL-1β and IL-6 involved in inflammatory skin diseases, in addition to inhibiting IgE-mediated degranulation, mast cell production, and histamine-induced vascular permeability[29].

Among secondary therapies, reports of an excellent response to treatment with omalizumab[11] indicate that anti-IgE is a safe and effective treatment for refractory physical urticaria. High doses of antihistamines are indicated in patients with refractory CU symptoms. In a multicenter trial, 2 doses were analyzed for efficacy and safety. Safe doses of 150 mg and 300 mg every 4 weeks showed high rates of positive outcomes at the end of treatment for complete and partial remission and a pronounced overall reduction in disease activity. Maintenance doses can be administered every 6 to 12 weeks. Omalizumab effectively reduces disease activity and stimulus-specific test responses; however, disease severity is not a predictor of treatment response. Omalizumab induces a long-term positive response and is well tolerated[10].

Other medications such as cyclosporine[35], anakinra (anti-IL1)[36], etanercept (TNF inhibitor)[37], and reslizumab (anti-IL5)[38] have shown beneficial responses in selected cases[11].

Cold desensitization, repeated exposure to progressively cooler conditions over a long period, also reduces patients' symptoms[11,12]. However, this treatment can provoke anaphylaxis during induction and should therefore only be performed under specialized medical supervision. The maintenance of tolerance requires daily cold baths; thus, adherence to the therapeutic procedure at home is low[11].

Prescribing self-injected epinephrine to groups at high risk of systemic reactions would be ideal if such groups can be identified. Individuals at high risk are described as those with a provocation test that shows a positive result in less than 3 min and those with laryngeal symptoms induced by exposure to cold foods or drinks[4]. When updating the recommendations for the diagnosis and treatment of acute and chronic urticaria, it was suggested for those who have CU to "Injectable epinephrine can be prescribed for patients judged to be at increased risk of systemic reactions"[39]. Obviously, the main indication is for those who have already experienced previous anaphylaxis due to this reason, though based on current evidence, we recommend injectable epinephrine for patients who are believed to be at high risk of systemic reactions.

Despite its rarity, recent studies indicate that most patients with this condition tend to present long-term disease, averaging 4.8 to 7.9 years[3], and almost half of patients achieve complete remission in 5 years[3,12]. Here, remission is defined as the absence of symptoms despite exposure to cold, and the discontinuation of any urticaria treatment for at least 6 months associated with a negative result in the provocation test[12].

CONCLUSIONS

Cold-induced urticaria is a complex disease with numerous variables, and professionals must be aware of these different conditions to recognize the risk of anaphylaxis in these patients. It is crucial to raise awareness concerning systemic reactions, with extensive investigation and proper treatment. Knowledge of these factors allows health professionals to establish early, adequate therapeutic strategies.

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