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CASE REPORT

Cholinergic Urticaria Associated with Acquired Generalized Hypohidrosis: Two Case Reports and Review of the Literature

Urticária Colinérgica Associada a Hipohidrose Generalizada Adquirida: Dois Casos Clínicos e Revisão da Literatura

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ABSTRACT – Cholinergic urticaria is a relatively common condition defined by itching, redness and whealing induced by exercise and passive warming. In turn, acquired idiopathic generalized anhidrosis is a rare disorder of unknown pathogenesis, characterized by an impairment in total body sweating despite exposure to heat or exercise. We report two cases of this extremely rare association of cholinergic urticaria and acquired generalized hypohidrosis, and briefly review current knowledge with regard to classification, ethiopathogenesis and therapeutic options.
KEYWORDS – Hypohidrosis/etiology; Urticaria/complications

RESUMO – *A urticária colinérgica é uma patologia relativamente comum definida por máculo-pápulas eritematosas e pruriginosas induzidas por aumento da temperatura corporal, passivo ou induzido por exercício físico. Pelo contrário, a anidrose generalizada idiopática adquirida é uma doença rara de patogénese desconhecida, caraterizada por um comprometimento da capacidade de sudação, apesar da exposição a calor ou exercício. Descrevem-se dois casos desta associação extremamente rara de urticária colinérgica e hipohidrose generalizada adquirida, e procede-se a uma breve revisão do conhecimento atual no que respeita à classificação, etiopatogenia e opções terapêuticas.*
PALAVRAS-CHAVE – *Hipohidrose/etiologia; Urticária/complicações.*

INTRODUCTION

Cholinergic urticaria (CU) is a type of chronic inducible urticaria clinically characterized by pinpoint-sized, highly pruritic wheals with surrounding erythema. The wheals are typically provoked by stimulus such as physical exercise, warmth, intake of spicy foods and emotional distress, which increases the body core temperature and promotes sweating.[1] The symptoms usually subside within one hour, however, most patients with CU complain of a stinging or tingling pain and/or itching at the onset of symptoms, which appear to highly disrupt their quality of life.[2] The diagnosis of CU is generally straightforward due to its characteristic clinical presentation. However, the underlying pathological mechanism is still not completely understood. CU is rarely accompanied by acquired anhidrosis and/or hypohidrosis, suggesting that sweat itself is not essential for the development of CU. Almost all patients with CU who develop acquired anhidrosis and/or hypohidrosis are assumed to have acquired idiopathic generalized anhidrosis.[3]

Acquired idiopathic generalized anhidrosis (AIGA) is a rare disorder characterized by inadequate sweating in response to heat, in the absence of apparent causative skin, metabolic, or neurological etiologies. This disorder affects predominantly young males and is often complicated by pain and/or paresthesia, severely disturbing quality of life.[4] Psychogenic sweating is usually preserved. Exposure of these patients to high temperatures often results in heat stroke, with symptoms such as general malaise, hyperthermia, dizziness, palpitations, fainting and ultimately loss of consciousness due to the dysregulation of body temperature.[5]

We report two cases of CU associated with acquired generalized hypohidrosis, both refractory to multiple treatments and with severe disruption of quality of life.

Case Reports

Case 1

A previously healthy young male presented in early 2020 a 1-year history of pinpoint-sized, pruritic wheals, initially circumscribed to the trunk, and later also affecting the limbs. They were associated with tingling pain and hyperthermia, and followed physical exercise, exposure to hot weather and emotional stress. He took cold showers to alleviate symptoms. His growth and development were normal. Sweating was normal till the present condition. In fact, shortly before the onset of the skin lesions, he noticed generalized anhidrosis and intolerance of hot environments, especially during summer. There were no episodes suggestive of heat stroke. He had no personal history of atopic diathesis. His familial history was unremarkable.

The following laboratory studies were all within the normal range: full blood count, urinalysis, serum protein electrophoresis, blood urea nitrogen, creatinine, C-reactive protein, fasting blood glucose, liver

enzymes, potassium, sodium and chloride ions and thyroid function. Anti-nuclear antibodies were positive (1:160 titer); other autoantibodies were negative. The Helicobacter pylori breath test was negative. Serologies to cytomegalovirus, Epstein-Barr virus and syphilis were also negative. Abdominal ultrasonography was normal. He visited a rheumatologist that did not find any clinical evidence of immune mediated disease.

The patient had been treated with second generation H1-antihistamines, with little benefit. Prednisolone was later introduced (20 mg initially, with tapering dosages) along with second generation H1--antihistamines up-dosing and montelukast, with limited effectiveness on both the anhidrosis and CU.

Case 2

A previously healthy young male presented in 2018 a 6-month history of pinpoint-sized, pruritic wheals, associated with stinging pain. The wheals appeared on the trunk and limbs following an increase in body core temperature, either by exposure to hot weather or physical exercise. He had a wet cloth with him at all times, that he applied on the skin to alleviate symptoms. He was unable to go to school, since the classrooms had no air conditioning. In summer he was confined to his home. His growth and development were normal. In one of the consultations his father mentioned that he no longer sweated. When asked, he had episodes suggestive of heat stroke. There was no personal or familial history of atopic diathesis. The pin-point lesions were observed whenever the air conditioning was turned off in the office.

The following laboratory studies were all within the normal range: full blood count, urinalysis, serum protein electrophoresis, blood urea nitrogen, creatinine, C-reactive protein, fasting blood glucose, liver enzymes, tryptase, immunoglobulins, potassium, sodium and chloride ions and thyroid function. Autoantibodies were negative. A skin biopsy from the axilla was performed, which showed no evidence of sweat gland atrophy, occlusion of the ducts or periglandular inflammatory infiltration.

The patient had been treated with second generation H1-antihistamines, with little benefit. Prednisolone was later introduced (up to 40 mg daily) along with second generation H1-antihistamines up-dosing, montelukast, ranitidine, propranolol and scopolamine butylbromide, with limited effectiveness on both the anhidrosis and the CU. Omalizumab treatment was initiated (300 mg with 4-week intervals), but after 5 months without clinical response it was discontinued. At this point, an intravenous high-dose (methylprednisolone 500 mg for 3 days) steroid pulse therapy was tried followed by oral prednisolone at 40 mg/day, but failed to produce any improvement in symptoms. A trial of oral cyclosporine was also attempted, again without any satisfactory results.

DISCUSSION

Several research groups have proposed four subtypes of CU based on the pathogenesis and clinical characteristics of this condition: (a) sweat allergy-type, (b) follicular-type, (c) CU with angioedema and/or anaphylaxis, and (d) CU with acquired anhidrosis and/or hypohidrosis.[4]

The conventional sweat-hypersensitivity type is characterized by non-follicular wheals, development of satellite wheals following local acetylcholine injection, a positive autologous sweat skin test result and a negative autologous serum skin test result.[6]

The follicular type is characterized by pinpoint wheals coincident with follicles, no development of satellite wheals following local acetylcholine injection, a positive autologous serum skin test result and lack of sweat allergy.[3]

CU with angioedema and/or anaphylaxis appears to be closely related to atopic diathesis, female gender and high prevalence of sweat allergy. Wheals in these patients often appear in eczematous lesions consistent with atopic dermatitis. These patients respond poorly to H1-antihistamines.[7,8]

It seems to be especially important to differentiate the subtypes described above from subtype (d), particularly in terms of the sweating function, since increasing reports suggest that the therapeutic approach should be different.[3]

As previously stated, it is assumed that almost all patients with CU who develop acquired anhidrosis and/or hypohidrosis have AIGA. No epidemiological data on AIGA has been published to date. Nevertheless, it is thought to be rare, as less than 200 cases have been reported in literature.[9] Patients with AIGA may be misdiagnosed as having other conditions since it is still an underrecognized disease.

The etiology and pathophysiology of AIGA seem to be heterogeneous. The most consensual mechanisms are (a) dysfunction or degeneration of cholinergic sympathetic nerve fibers involved in sweating (sudomotor neuropathy), (b) dysfunction of acetylcholine receptors and/or cholinergic signals, and (c) sweat gland failure, namely poral occlusion.[9] In the first two mechanisms, the anhidrosis results in histological degeneration; in the latter, the destruction of sweat glands results in anhidrosis. These conditions cannot be differentiated at present, but the latter has a more prolonged clinical course.[5]

Sudomotor neuropathy is believed to affect only sudomotor function without causing any other types of neuropathy. Possible sites of dysfunction include the hypothalamus, the medulla oblongata/spinal cord, and the preganglionic and postganglionic sympathetic efferent fibers.[10]

Decreased expression of the muscarinic acetylcholine M3 receptor (CHRM3) in the sweat glands has been observed in patients with AIGA, as well as reduced expression of acetylcholine esterase.[11] These findings suggest that there is an excess of acetylcholine that cannot interact with cholinergic receptors, resulting in the stimulation of sensory nerve terminals, which produces pain and acts on CHRM3 in mast cells around the sweat glands, causing wheals. The involvement of autoantibodies to the muscarinic acetylcholine M3 receptor in sweat glands has been proposed as the underlying mechanism.[12]

Anhidrosis in sweat gland failure is a result of primary immunological destruction of sweat glands, which may comprise many heterogeneous pathological conditions, poral occlusion being one of them.[5] Kobayashi *et al* reported two patients whose biopsies showed occlusion of the superficial acrosyringium.[13] They proposed that the occlusion and subsequent leakage of sweat from the sweat ducts were responsible for the development of the disease, since sweat contains several inflammatory enzymes and cytokines which can induce local inflammation.

Diagnostic criteria for AIGA have been published by Munetsugu *et al*.[5] They establish the diagnosis of AIGA when anhidrotic or hypohidrotic areas affect 25% or more of the entire body, the lesions are widely distributed in a non-segmental spinal pattern, and no other autonomic or neurological symptoms are observed.

The anhidrotic or hypohidrotic areas can be detected by the thermoregulatory sweat test or by thermography.[5] The thermoregulatory sweat test based on the Minor method using the iodine-starch reaction is the most commonly performed and easy to interpret, since the

areas that do not turn black are the anhidrotic or hypohidrotic ones. When thermography is performed in combination with the thermoregulatory sweat test, areas of increased body temperature are found to correspond to anhidrotic areas.[5] Both these tests are not widely available.

In recent years, some authors have proposed that the therapeutic approach to CU should be distinct depending on whether there is sweating dysfunction or not.[3] Pharmacological therapy and avoidance of causative factors are standard approaches for CU.[14]

Second generation H1-antihistamines are first-line therapy for patients with CU, but their efficacy is often limited, either with standard or increasing doses.[15] The addition of an H2-receptor antagonist has been reported to be effective in patients with refractory CU unresponsive to up-dosing of an H1-receptor antagonist.[2] Other studies have demonstrated the efficacy of scopolamine butylbromide,[16] propranolol and montelukast.[17] Omalizumab has been reported to be effective for severe CU, although treatment failure has also been reported.[18]

High doses of danazol (600 mg daily) have been reported to be effective. However, the side-effect profile of danazol restricts its use, and dosing should be minimized.[14]

Topical application of keratolytic agents is reportedly effective in treating hypohidrotic CU associated with the occlusion of sweat ducts.[19]

Despite insufficient level of evidence, systemic administration of corticosteroids is recommended for management of early onset AIGA and concurrent cholinergic urticaria, on the basis of findings presented in numerous case reports.[4,5,20] However, patients with delayed treatment initiation or degeneration of sweat gland tissue may respond poorly.[5] The most common forms of steroid therapy include steroid pulse therapy alone (1-2 courses of a 3-day intravenous infusion of methylprednisolone at a dose of 500-1000 mg/day), steroid pulse therapy followed by oral prednisolone at 30-60 mg/day, and oral prednisolone at 30-60 mg/day followed by dose tapering. Nevertheless, the evidence regarding appropriate doses and administration routes is still not very robust. A trial of oral immunosuppressants may be considered in patients who do not respond to steroid therapy.[5]

Desensitization protocols involving regular physical exercise and/or bathing or treatment with autologous sweat in patients with sweat allergy-type CU have been described.[13,21,22] Very recently, Minowa *et al*[23] published a retrospective medical record review of 27 patients where they found that regular sweating activities, alone or with second generation antihistamines or steroid pulse, provided symptom relief in 92% of the patients, and the effects of regular sweating activities were rapidly established (median time of 1.5 months).

Our first patient was diagnosed very recently and is still going through the therapeutic steps proposed by the EAACI consensus recommendations.[14]

In our second patient, since the EAACI treatment guidelines proved ineffective, steroid pulse therapy was attempted. It also failed to produce results, and we can speculate that one possible reason for that was delayed treatment initiation. The good results reported by Minowa *et al*[23] in their desensitization protocol gives a new hope and will be considered for this patient in the near future.

Munetsugu *et al*[5] have proposed an algorithm for the treatment of AIGA. After the diagnosis, the disease should be adequately explained to patients, so that they understand the high risk of heatstroke due to the thermoregulatory disorder associated with decreased sweating. As part of lifestyle guidance, patients should be instructed on techniques for preventing heatstroke. When AIGA is severe (area of anhidrotic/hypohidrotic lesions >75% and area of painful skin or wheals >75%), steroid therapy should be considered (recommendation grade: C1). Steroid therapy should also be considered for patients with pain or symptoms of heatstroke that disrupt daily life or work.[5]

CONCLUSION

The available evidence suggests that various pathological mechanisms contribute to the development of AIGA. Depending on the different etiologies, the clinical courses appear to be distinct. However, at present it is not possible to clarify the specific underlying mechanism responsible for each AIGA case.

CU associated with acquired generalized hypohidrosis is an acknowledged clinical entity, although still underrecognized, underreported and, unfortunately, often refractory to the available therapies. Systemic corticosteroids are unquestionably the most effective therapeutic option. However, many patients are resistant to corticosteroids and/or experience recurrence. It is imperative to develop novel alternative therapies, as these patients suffer great deterioration in quality of life.

To our knowledge, these are the only cases of cholinergic urticaria associated with acquired generalized hypohidrosis reported in our country. Furthermore, we did not find in PubMed any other published reports of similar cases in Europe.

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