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CHOLINERGIC URTICARIA: A REVIEW FROM PATHOPHYSIOLOGY, SYMPTOMS, SUBTYPES, DIAGNOSIS TO TREATMENT

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Abstract: Cholinergic Urticaria (CU) first described by Duke, as a subset of the physical urticarias. It predominantly affects young adult population after the age of 20. Manifestions are small (2 to 5 mm) punctate papules surrounded by an erythematous halo, beginning on the upper thorax and neck but may spread to the entire body. Often, however, only a pruritic macular erythema of skin can occur. Lesions may persist from 15 to 20 minutes to several hours. If stimulus persists, the hives may coalesce and resemble angioedema, but vascular collapse is rare. Pulmonary symptoms often occur but significant changes on peak flow measurements are not always reproducible. The symptoms are known to occur in response to exercise, passive body warming and emotional stress. CU can be idiopathic or related to hyperhydrosis, hypohydrosis and/or anhydrosis. A rise in plasma histamine levels due to mast cell degranulation has been demonstrated in symptomatic patients with a significant etiological role of acetylcholine. The diagnosis of cholinergic urticaria may be confirmed by a thorough clinical evaluation including specialized tests that induce the development of hives (urticarial wheals) such as a heat challenge. Differential diagnosis includes exercise-induced anaphylaxis idiopathic cold urticaria, mastocytosis, cardiovascular disorders, food allergy exacerbated by exercise, and angioedema.CU can be managed by combination of first line treatment and non pharmacological measures according to the subtypes. Effective drug therapy includes antihistamines, UV light, danazol beta-blockers, leukotriene inhibitors, omalizumab, corticosteroids, leukotriene receptor antagonists in combination with antihistamines. This article reviews the aggravating factors, subtypes, symptoms, pathophysiology, role of acetylcholine, diagnosis, and treatment of CU.

Keywords: Physical urticaria, Cholinergic urticaria, Hyperhydrosis, Hypohydrosis, Anhydrosis, Acetylcholine.

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INTRODUCTION

Cholinergic urticaria, a subcategory of physical urticaria, is characterized by a hypersensitive skin response as a result of increase body temperature (passively or actively), or the precipitating release of sweat. It is associated with a significant level of disability similar to severe atopic dermatitis and is much greater than psoriasis or acne based on Dermatology Life Quality Index. [1] In the general population about half of the cases of chronic urticaria which lasts for > 6 weeks, are due to physical urticaria. Physical Urticaria occurs in response to a wide variety of physical triggers which may be mechanical, thermal or solar like hot water, heat, cold, exercise, sunlight, pressure, and vibration. Thus different types of physical urticaria are: acquired, cold urticaria, delayed-pressure urticaria, solar urticaria, vibratory urticaria, urticarial dermatographism and cholinergic urticaria, out of these cholinergic urticaria is second most common after dermographic urticaria. Of those with CU, exercise is the most provocative factor, able to cause an outbreak in 89%. [2]

Population Affected and Prevalence

With prevalence of 11.2% among the young adult population, the majority of the cases of CU occur over the age of 20, equally affecting males and females and the incidences peak between 26 and 28 years of age. [2] Thirty percent of patients with physical urticarias have CU. [3]

Precipitating factors

Stimulation of the cholinergic sympathetic innervation of sweat glands causes CU. An increase of the body core temperature and not an external stimulus notably leads to elicitation of symptoms. The most frequent causes of increase in core body temperature leading to CU are shown in table 1.

Table: 1

The Most Frequent Causes Of Increase In Core Body Temperature Precipitating CU [4]
Hot bath (69%)
Sweating (56%)
Physical exercise (47%)
Emotional responses (sadness, anxiety, anger, laughter) (20%)
Sometimes warm or spicy food (9% and 2% respectively)
Alcoholic beverages (9%),

Apart from those shown in table 1, transitioning from a cool to a hotter environment without allowing the body time to slowly acclimate to the temperature difference such as walking from a cold room to a hot room can precipitate CU. Physical urticarias are not known to be related to specific occupations, but cholinergic urticaria and delayed - pressure urticaria may get precipitated or aggravated by heavy work in occupational settings. A familial tendency has also been reported. [5] It may occur in combination with other physical urticarias such as dermatographism (whealing which is induced by shearing forces on the skin), and cold urticaria. [6]

Symptoms

CU manifested by appearance of extremely itchy, small (2 to 5 mm) circular hives (pruritic urticaria) that have well-defined borders and pale (blanched) centers. These are usually surrounded by an erythematous halo i.e., areas around these skin lesions become intensely red (wheal-and-flare reaction). The symptoms occur in association with exercise, hot showers, sweating , and/or anxiety. Often, however, only a pruritic macular erythema covers an area of skin 10 to 20 cm in diameter. Small hives occur most frequently on the upper back, upper arms, and/or neck and but may spread to the entire body. A single lesion typically persists for 15 to 20 minutes, although the episode producing many lesions may last for minutes or up to an hour. Urticarial lesions may coalesce to form larger red areas, giving the skin a "blushed" appearance. Some individuals with cholinergic urticaria may have swelling (angioedema) of the eyelids, lips, hands, and/or feet. A small number of people with cholinergic urticaria may also experience a variety of systemic symptoms including abdominal cramps, flushing, diarrhea, faintness, general weakness, asthma, and/or excessive sweating (hyperhidrosis) but vascular collapse is rare. [7] Pulmonary symptoms often occur [7,8] but significant changes on peak flow measurements and pulmonary function tests are not always reproducible.

Subtypes

Three subtypes of CU are known.

First is Sweat hypersensitivity subtype of CU. It refers to those who are hypersensitive to their own sweat. The hives are observed to coincide with perspiration points of sweating.[9] Diagnosed by a positive reaction to an intradermal injection of autologous sweat.[10]

Second, acquired anhidrosis and/or hypohidrosis refer to those who have abnormally reduced sweating. Severe heat intolerance (e.g., nausea, dizziness and headache), and tingling, pricking, or burning pain over the entire body on exposure to hot environments or prolonged exercise which improve after cooling the body. Occurs in the absence of any causative skin, metabolic, or neurological disorders. [11] Failure of the topical indicator such as iodinated starch or sodium alizarin sulphonate to undergo a colour

change during thermoregulatory sweat testing through the use of a hot box / room, thermal blanket or exercise can indicate anhidrosis and/ or hypohidrosis (see minor test). [12] Sweat glands or ducts reveal cellular infiltrates in skin biopsy. [9]

Idiopathic CU, those patients who do not fall under any of the above categories i. e., patients without any clue to diagnosis are categorized into this third subtype idiopathic CU.

Pathophysiology

Degranulation of mast cells with release of histamine is central to the development of wheals and angioedema. Urticaria is due to a local increase in permeability of capillaries and venules. These changes are dependent on activation of the cutaneous mast cells, which contain a range of mediators predominantly histamine Histopathologically chronic urticaria is characterized by an inflammatory infiltrate comprising of CD4+ and CD8 + T lymphocytes, eosinophils, basophils and neutrophils.

Tanaka et al. found that the sweat hyper –sensitivities of CU and atopic dermatitis seem to be virtually the same, and therefore, the sweat-induced histamine release from basophils may also be mediated by a specific IgE for sweat in atopic dermatitis as well as CU. [9]

In cases of acquired anhidrosis and/or hypohidrosis the wheals, hypohidrosis, and pain seems to result from the low expression levels of acetylcholinesterase (AchE) and cholinergic receptor muscarinic 3 (CHRM3) in the eccrine gland epithelial cells. Elevated expression levels of CCL2/MCP-1, CCL5/RANTES and CCL17/TARC which result in chemoattracted CD4+ and CD8+ T cell populations to the surrounding area may be responsible for exerting a downmodulatory effect on the AchE and CHRM3 expressions. Corticosteroid inhibits the expressions of CCL2/MCP-1, CCL5/RANTES and CCL17/TARC. This further support the notion that CCL2/MCP-1, CCL5/RANTES and CCL17/TARC play a crucial role. [13]

CU And Acetylcholine

It is believed that acetylcholine plays an essential role in the development of CU. In experimental models of rat acetylcholine induces degranulation of mast cells. [14,15] Clinically induced sweating and numerous pin-point hives, similar to CU, are produced on subcutaneous injection of a cholinergic agent, carbaminoylcholine. [16] In vitro assay with LAD2 cells, a human mast cell line showed that acetylcholine dose dependently induced the degranulation of the mast cells, suggesting an essential role of acetylcholine in the development of CU.

Diagnosis

The diagnosis of cholinergic urticaria may be confirmed by a thorough clinical evaluation including specialized tests that induce the development of hives (urticarial wheals). About 30 percent of people with this disease develop hives when a cholinergic drug such as nicotine or acetylcholine is injected directly into the skin (intradermal). A heat challenge such as immersing an arm in warm water or exercising while wearing warm clothing may also help to confirm the diagnosis of cholinergic urticaria. During a systemic attack of cholinergic urticaria, the level of histamine may be elevated in the fluid surrounding the skin lesion (plasma histamine).[17]

Differential Diagnosis

Diagnostic considerations for cholinergic urticaria includes, Exercise-induced anaphylaxis idiopathic cold urticaria, mastocytosis, cardiovascular disorders, food allergy exacerbated by exercise, and angioedema.

Exercise-induced anaphylaxis produces giant hives. Passive heat challenges are valuable in differentiating between cholinergic urticaria and exercise-induced anaphylaxis. In cholinergic urticaria, passive heating such as from hot baths or saunas causes histamine release, urticaria, and anaphylactic symptoms. In contrast, patients with exercise-induced anaphylaxis do not react with passive heating.

Idiopathic cold urticaria is a form of physical urticaria characterized by the development of urticaria and / orangioedema after cold exposure.

Patients with mastocytosis are susceptible to anaphylaxis from various triggers, including exercise. A useful distinguishing feature between exercise-induced anaphylaxis and mastocytosis is the serum tryptase level. Patients with mastocytosis have persistent elevation in serum tryptase levels, whereas patients with anaphylaxis from other causes demonstrate elevation of tryptase only during acute attacks.

Cardiac can cause sudden fatigue, dyspnea, and vascular collapse during exercise. However, cardiovascular disorders do not cause pruritus, urticaria, angioedema, and laryngeal edema.

Patients with food allergy may have more severe and frequent reactions with concomitant exercise. In the case of food-dependent exercise-induced anaphylaxis, demonstrating that patients can tolerate the offending food in the absence of physical activity is essential. A formal food challenge may be helpful in this regard.

Hereditary angioedema is an inherited disease resulting from a deficiency or dysfunction of the C1 inhibitor enzyme (C1-INH). Acquired angioedema is caused by autoimmune

interference with C1-INH function. [18] A key distinction between hereditary or acquired angioedema and exercise-induced anaphylaxis is the absence of urticaria and pruritus in hereditary and acquired angioedema.

Treatment

In cholinergic urticaria, rapid and prolonged control of symptoms so as to provide better quality of life is the primary goal of treatment. Identification and avoidance of known triggers are the first steps in the management. CU is thought to carry a good prognosis.

For sweat hypersensitivity subtype of CU proposed first-line treatment is rapid desensitization protocol using autologous sweat. [10] Non-pharmacological treatment includes forced perspiration by excessive body warming (hot bath or exercise) used daily may reduce the symptoms through exhaustion of inflammatory mediators. [19] Antihistamines are a commonly prescribed first-line treatment for conventional urticaria, but its effectiveness in the treatment of CU is rather limited in most cases. Treatment(s) with mixed success are danazol ,[20, 21] anti-IgE therapy, [22] propranolol ,[23] and antileukotriene.

In acquired anhidrosis and/or hypohidrosis subtypes, first-line treatment is steroid pulse therapy such as methylprednisolone. [24] Non-pharmacological treatment in the absence of sweat, cold -water sprays and wet towels can be used increase the evaporative loss of heat from the skin. Shifting to a cooler or air-conditioned environment when necessary can also reduce discomfort. In the event of severe hyperthermia (body temperature >106 °F/41 °C), drastic measures such as immersion in ice-cold water are necessary to prevent irreversible brain damage. [25]

For Idiopathic subtype, treatment can be started with a second generation non sedating (or less sedating) antihistamines like cetirizine, loratidine, fexofenadine, astemizole, mizolastine, ebastine etc. UV light has been beneficial in some patients with cholinergic urticaria, but there are contraindications to UV light.

Ketofen may be helpful in patients with both cold urticaria and cholinergic urticaria. Benzoyl scopolamine administered topically and scopolamine butylbromide administered orally may be helpful in blocking the appearance of cholinergic urticaria lesions after challenge. [26] Montelukast and immunosuppressive agents such as omalizumab are other treatment options.

CONCLUSION

Patients with CU are often frustrated and anxious. Education and reassurance are critical components of successful management and should begin as soon as the diagnosis is made. CU shows a good prognosis and better quality of life can be provided to the

patient with non pharmacological measures and drug therapy without precipitation of outbreaks. We emphasize that clinician should differentiate exercise- induced cholinergic urticaria from life threatening exercise-induced anaphylaxis.

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