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SHORT REPORT

Cholinergic urticaria: pathogenesis-based categorization and its treatment options

S. Nakamizo, G. Egawa,* Y. Miyachi, K. Kabashima

Department of Dermatology, Kyoto University, Kyoto, Japan
*Correspondence: G. Egawa. E-mail: gyohei@kuhp.kyoto-u.ac.jp

Abstract

Background Cholinergic urticaria (CU) has well-described characteristic clinical presentations, yet the precise pathological mechanism remains incompletely understood. A variety of pathogeneses has been proposed, which suggests that there exists several clinical subtypes.

Conclusions In this review, we categorize CU into four subtypes: (i) CU with poral occlusion; (ii) CU with acquired generalized hypohidrosis; (iii) CU with sweat allergy; and (iv) idiopathic CU, and discuss diagnostic and treatment options.

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Introduction

Cholinergic urticaria (CU) is one of the physical urticaria characterized by small and pruritic weals which follow sweating events, including elevation of body temperature, physical exercise, intake of spicy foods and emotional strains. To make the diagnosis of CU is generally not difficult because of its characteristic clinical manifestations. However, the underlying pathological mechanism remains incompletely understood. CU is sometimes accompanied by acquired generalized hypohidrosis (AGH), suggesting that the sweat itself is not essential for the initiation of CU. Recently, we and others have revealed that the disturbance of muscarinic cholinergic receptors (CHRMs) expression is involved in the development of CU associated with AGH. In this review, we will present an overview of the current range of our knowledge on the pathological mechanisms of CU and its treatment options, and propose a simple categorization based on its pathogenesis.

The essential role of acetylcholine in the development of cholinergic urticaria

The sweat glands receive sympathetic innervations but express muscarinic acetylcholine receptors, which are normally expressed on parasympathetic nervous systems; therefore, acetylcholine is considered to be a central signal mediator for the secretion of sweat. Previous reports have demonstrated that subcutaneous injection of cholinergic agents induce sweating and the development of numerous pin-point hives in patients with CU, and that the symptoms of CU are inhibited by prior atropinization of the skin.[1] In addition, recent studies have shown that not only sweat glands but also mast cells express muscarinic cholinergic receptor 3 (CHRM3), which is a responsible cholinergic receptor for sweating.[2] In fact, acetylcholine triggers degranulation of rat mast cells.[3] Although it remains unknown whether this is applicable even in human,[3] acetylcholine seems to play an essential role in the development of CU.

The minor role of histamine in the pathogenesis of cholinergic urticaria

Previous studies have reported that serum histamine levels are elevated in the presence of weals and are further increased by hard exercise in some patients with CU.[4] These findings suggest that histamine plays at least some roles in the pathogenesis of CU. However, serum histamine levels are not elevated in all CU patients and are not correlated with the severity of symptoms.[5] In addition, in contrast to conventional urticaria, the effect of antihistamine drugs is rather limited in most cases of CU, suggesting that histamine plays only a minor role in the pathogenesis of CU. The potential involvement of additional mediators apart from histamine, such as serotonin, bradykinin and eosinophil chemotactic agents has been postulated.[4,6]

Cholinergic urticaria due to poral occlusion

There are several cases suggesting that CU is caused by poral occlusion.[7] In such cases, occlusion of superficial acrosyringium due to keratotic plugs and dilatation of sweat ducts are evident by histological examination. Such interferences of sweat secretion sometimes cause hypohidrosis. Kobayashi *et al.* hypothesized that poral occlusion leads to the leakage of sweat which contain numerous enzymes, such as renin-like substances, secretory IgA, IgE and cytokines including interleukin 1α and β, and interleukin 8 that, in turn, induce local inflammation and cause weals.[7] In line with this hypothesis, an intradermal test with cholinergic agents was negative, and did not induce any wheal in CU with poral occlusion.[7] The symptoms are usually exacerbated in winter and resolved in summer,[7] suggesting that daily sweating in summer may inhibit the formation of keratotic plugs to prevent the occurrence of CU. Most cases of this type were reported in Asia and a very rare cause for CU in Europe; therefore, CU due to poral occlusion may relate to Asian and/or to hot and humid climate.

Cholinergic urticaria associated with acquired generalized hypohidrosis

It is well known that CU is sometimes accompanied by AGH.[8] A variety of etiologies, including autoimmunity to sweat glands or to acetylcholine receptors,[9] degeneration of post-ganglionic sympathetic skin nerve fibres and poral occlusion (see above) have been proposed as causes of AGH.[10] Although it remains unknown how AGH induces CU, recent studies have shed light on the function of CHRMs. As described above, both sweat glands and mast cells express CHRM3. Intriguingly, Sawada *et al.* have reported that CHRM3 was decreased on sweat glands but not on mast cells in the CU patient with AGH.[2] Moreover, histological examinations of AGH sometimes show the increased expression of CHRMs on mast cells.[10] These findings raise the following hypothesis: In AGH patients, the interfered sweat production may cause the elevation of local acetylcholine levels. Consequently, excess acetylcholine stimulates sensory nerve terminals to produce pain and acts on the muscarinic CHRM3 on mast cells in the vicinity of sweat glands to cause weals. In accord with this hypothesis, an intradermal test with cholinergic agents was typically positive in this type of CU.[1] However, we experienced a case of CU patients with AGH which showed the absence of CHRM3 expression even on mast cells,[11] suggesting that some molecules other than acetylcholine may involve the development of CU. The symptoms in this type of CU occur all year round, but are more common in summer.

Cholinergic urticaria with sweat allergy

There are several studies suggesting that CU can be induced by an allergy to the components of human sweat. Adachi *et al.* have demonstrated that some CU patients showed immediate-type hypersensitivity reactions to their own diluted sweat by intradermal tests, and that basophils from these patients reacted to autologous sweat and released high amounts of histamine *in vitro*.[12] In addition, they reported the presence of specific IgE to sweat in CU patients, but not in normal controls. These reports imply the involvement of an allergic mechanism to autologous sweat in the pathogenesis of CU. However, since sweat itself includes inflammatory enzymes and cytokines as described above, the possibility of a non-allergic mechanism involved in this process has still not been clearly excluded.

Idiopathic cholinergic urticaria

We described three major causes of CU above; however, there still remain CU patients not applicable to these categories. We have categorized such patients into idiopathic CU tentatively in this review. Further categorization of the idiopathic CU should be addressed in the future.

Categorization of cholinergic urticaria based upon pathogenesis

Based on the above observations, CU can be categorized into at least four subtypes: (i) CU with poral occlusion; (ii) CU with AGH; (iii) CU with possible sweat allergy; and (iv) idiopathic CU. Intradermal tests and histological examinations are useful for making the differential diagnosis. Hyperreactivity to cholinergic agents is observed in CU with AGH. Positive results of an intradermal test with diluted autologous sweat may support the diagnosis of sweat allergy-associated CU. Obstruction of the acrosyringium by keratotic plugs and dilatation of sweat duct are observed histologically in CU with poral occlusion. While moderate lymphocytic infiltration can be observed in all types of CU, atrophic sweat glands are occasionally the characteristics of CU with AGH. Seasonal exacerbation is informative: Poral occlusion tends to occur

Table 1 Cholinergic urticaria: pathogenesis-based categorization and its treatment options

Subtype	Season	Intradermal test for cholinergic agent	Sweat allergy	Hypohidrosis	Pathology	Treatment
Poral occlusion	Severe in winter	Typically negative	Negative	Occasional	Keratinizing and sweat duct ectasia	Bathing, keratolytic agents,
AGH	All year round	Positive	Negative	Always	Normal or cell invasion	Systemic steroid therapy
Sweat allergy	—	Positive	Positive	None	Normal or keratinizing	Anti-IgE therapy desensitization
Idiopathic	—	Negative	Negative	None	Normal or cell invasion	Antihistamine drugs

in winter when sweating is not frequent, and other subtypes are exacerbated in summer when more sweating occurs in accord with acetylcholine production.

Treatment options based on cholinergic urticaria pathogenesis

In general, anti-histamine drugs are the first choice for the patient of CU, though most patients show only mild to moderate responses.[13] Anti-cholinergic drugs, such as scopolamine, have been used, however, they shows only minor effects.[14] Various other therapeutic approaches, including the use of danazol,[15] β2-adrenergic stimulants,[16] and β2-adrenergic blockers,[17] have been reported, yet the effectiveness of each therapy varies and does not reach the standard agreement.

There are several therapeutic approaches which are based on the cause of CU (see Table 1). In CU patient with poral occlusion, repeated sweating caused by a hot bath or exercise may improve CU symptoms.[7] In fact, CU with poral occlusion resolves in summer when sweating is frequently induced. It is probably due to preventing the formation of keratotic plugs or recanalization of occluded sweat duct. Repeated sweating is sometimes effective also for CU with sweat allergy, which may be associated with desensitization of autologous sweats. Indeed, there is a case report that CU with sweat allergy has been successfully treated by repeated desensitization with partially purified sweat antigen.[18] The application of anti-IgE antibody (omalizumab; 300 mg every 2 weeks) was also effective for some case of CU with sweat allergy,[19] supporting the involvement of IgE-mediated allergy in the development of CU. In CU patients with autoimmune-based AGH, systemic steroid therapy generally improves sweating as well as CU symptoms.[8,9] Intravenous high-dose (500–1000 mg) steroid pulse therapy can be a choice for severe cases of CU with autoimmune-based AGH.

At present the pathogenesis of CU is not completely clarified; therefore, some of CU patients may overlap or may be categorized into idiopathic CU. Further studies and accumulation of case reports are necessary for the improvement of pathogenesis-based treatments for CU.

References

1 Horikawa T, Fukunaga A, Nishigori C. New concepts of hive formation in cholinergic urticaria. *Curr Allergy Asthma Rep* 2009; **9**: 273–279.

2 Sawada Y, Nakamura M, Bito T *et al.* Cholinergic urticaria: studies on the muscarinic cholinergic receptor M3 in the anhidrotic and hypohidrotic skin. *J Invest Dermatol* 2010; **130**: 2683–2686.

3 Fantozzi R, Masini E, Blandina P, Mannaioni PF, Bani-Sacchi T. Release of histamine from rat mast cells by acetylcholine. *Nature* 1978; **273**: 473–474.

4 Soter NA, Wasserman SI, Austen KF, McFadden ER Jr. Release of mast-cell mediators and alterations in lung function in patients with cholinergic urticaria. *N Engl J Med* 1980; **302**: 604–608.

5 Kaplan AP, Gray L, Shaff RE, Horakova Z, Beaven MA. *In vivo* studies of mediator release in cold urticaria and cholinergic urticaria. *J Allergy Clin Immunol* 1975; **55**: 394–402.

6 Kaplan AP, Beaven MA. *In vivo* studies of the pathogenesis of cold urticaria, cholinergic urticaria, and vibration-induced swelling. *J Invest Dermatol* 1976; **67**: 327–332.

7 Kobayashi H, Aiba S, Yamagishi T *et al.* Cholinergic urticaria, a new pathogenic concept: hypohidrosis due to interference with the delivery of sweat to the skin surface. *Dermatology* 2002; **204**: 173–178.

8 Nakazato Y, Tamura N, Ohkuma A, Yoshimaru K, Shimazu K. Idiopathic pure sudomotor failure: anhidrosis due to deficits in cholinergic transmission. *Neurology* 2004; **63**: 1476–1480.

9 Nakamizo S, Miyachi Y, Kabashima K. A case of cholinergic urticaria associated with acquired generalized hypohidrosis and abnormal neurological findings: association with incomplete Ross syndrome? *Br J Dermatol* 2010; **162**: 903–905.

10 Shelley WB, Shelley ED, Ho AK. Cholinergic urticaria: acetylcholine-receptor-dependent immediate-type hypersensitivity reaction to copper. *Lancet* 1983; **1**: 843–846.

11 Nakamizo S, Kurosawa M, Sawada Y *et al.* A case of cholinergic urticaria associated with acquired generalized hypohidrosis and reduced acetylcholine receptors: cause and effect? *Clin Exp Dermatol* 2010; DOI: 10.1111/j.1365-2230.2011.04015.x.

12 Adachi J, Aoki T, Yamatodani A. Demonstration of sweat allergy in cholinergic urticaria. *J Dermatol Sci* 1994; **7**: 142–149.

13 Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol* 1994; **31**: 978–981.

14 Tsunemi Y, Ihn H, Saeki H, Tamaki K. Cholinergic urticaria successfully treated with scopolamine butylbromide. *Int J Dermatol* 2003; **42**: 850.

15 La Shell MS, England RW. Severe refractory cholinergic urticaria treated with danazol. *J Drugs Dermatol* 2006; **5**: 664–667.

16 Kennes B, De Maubeuge J, Delespesse G. Treatment of chronic urticaria with a beta2-adrenergic stimulant. *Clin Allergy* 1977; **7**: 35–39.

17 Feinberg JH, Toner CB. Successful treatment of disabling cholinergic urticaria. *Mil Med* 2008; **173**: 217–220.

18 Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Hide M. [Cholinergic urticaria successfully treated by immunotherapy with partially purified sweat antigen]. *Arerugi* 2007; **56**: 54–57.

19 Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy* 2008; **63**: 247–249.