TEMPERATURE THRESHOLDS AND CLINICAL COURSE OF PATIENTS WITH ACQUIRED COLD CONTACT URTICARIA

ME. Martinez-Escala, L. Curto-Barredo, Ll. Carnero, RM Pujol, A. Giménez-Arnau
Department of Dermatology. Hospital del Mar, Parc de Salut Mar. Universitat Autònoma de Barcelona. Barcelona. Spain

INTRODUCTION

Acquired cold urticaria is a chronic physical urticaria characterized by wheals and/or angioedema after exposure to cold air, liquids or solids[1]. Hives are caused by release of histamine, platelet activating factor, leukotriens and other proinflammatory mast-cell mediators in response to exposure to cold temperatures[2]. It is the forth commonest type of chronic urticaria after chronic spontaneous, dermographic urticaria and cholinergic urticaria. Symptoms are usually limited to cold-exposed skin areas, but extensive cold contact may result in generalized urticarial symptoms as headache, dyspnoea, hypotension and loss of consciousness[3]. Cold stimulation standardized tests are mandatory to confirm the diagnosis. The assessment of thresholds, critical time and temperature (CsTT and CTT), is recommended being useful to define severity. The classic diagnosis is based in the ice-cube test, and currently, more objectively method is performed with Peltier effect-based electronic device Temp Test® (Emo Systems, GmbH, Berlin, Germany)[4]. The latter allows determining disease activity and monitoring their response to therapeutic interventions[5].

OBJECTIVE

Our purpose is to describe the advantage of determining the temperature threshold in the assessment of the clinical course of patients with typical acquired cold urticaria.

PATIENTS AND METHODS

A prospective observational study was performed. Nineteen consecutive patients with a confirmed diagnosis of idiopathic acquired cold urticaria studied at the Hospital del Mar, from 2009 – 2010, were included. Exclusion criteria were based on patients under antihistaminics, glucocorticoids and immunosupressants agents for less than four weeks. Pregnants or patients with pregnancy desire were also excluded. The idiopathic nature of acquired cold urticaria was assessed after exclusion of conditions known to be associated with this disease. The diagnosis was confirmed by provocation testing with ice-cube and Temp Test® 3.0 (Emo Systems, GmbH, Berlin, Germany). Twenty milligrams daily of rupatadine were prescribed for continuous treatment for one year[6,7]. Patients underwent thresholds assessment by Temp Test® 3.0. Critical temperature (CTT) and critical stimulation time threshold (CsTT) at the time of enrolment and at the end of the treatment period. Patients were followed every three months during all study. This therapeutic approach is in agreement with our previous experience treating acquired cold contact urticarial with non-sedative anti-H1 antihistamines[7].

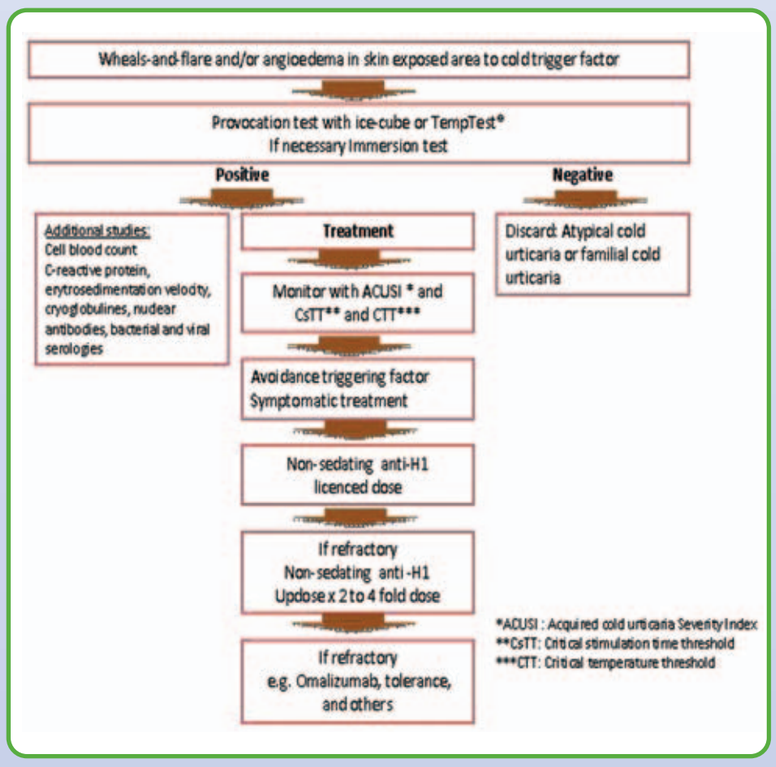
RESULTS

Ten women and nine men were admitted, with a mean age of **45** year-old (28 – 68 year-old). Mean cold urticaria duration was **5** years (1 – 22 years). Mean CsTT at the baseline was **2** minutes and **30** seconds (1 – 3.5 minutes) and the CTT was **13,6**ºC (26 – 4ºC). After one year of treatment with a daily dose of **20** mg of rupatadine, an elongation of **39.84%** (1.86 min) of CsTT, and a reduction of **60%** (8ºC) of CTT were observed. After one year of continuous treatment with non-sedative anti H1 all patients showed a CTT reduction. Thirteen were free of symptoms during their daily activities showing a complete response with undetectable thresholds. Two of the six remaining patients demonstrated more than **50%** CTT reduction with longer CsTT and clinically, the symptoms appeared just in risky situations. The other four patients showed just ≤ **30%** CTT reduction with little longer CsTT and clinically were symptomatic. No side effects were detected during rupatadine treatment in all the nineteen patients.
Two patients did not adhere to treatment with a daily dose of rupatadine, and it was taken on demand. Both have active disease at the end of the study, and demonstrated no-improvement on their temperature and critical time threshold.

Table 1. Characteristics and obtained results from nineteen patients. Patients 12 and 15 did not adhere to daily rupatadine intake.

Patients	Gender	Age	Disease's duration	Initial CsTT (sec)	Final CsTT (sec)	Elongation sec (%)	Initial CTT (ºC)	Final CTT (ºC)	Reduction ºC (%)	Evolution
1	F	48	1	90	180	90 (50)	14	10	4 (29)	Active
2	F	38	12	210	>300	91 (30)	8	<4	5 (63)	Active
3	F	37	2.5	150	>300	151 (50)	14	>6	7 (57)	Cure
4	F	55	22	210	>300	91 (30)	12	<4	9 (75)	Cure
5	F	52	2.5	150	>300	151 (50)	18	<4	15 (83)	Cure
6	M	51	8.5	210	>300	91 (30)	4	<4	1 (25)	Cure
7	M	43	3.5	150	>300	151 (50)	16	<4	13 (81)	Cure
8	M	40	2	<60	240	181 (60)	24	4	21 (87)	Active
9	M	52	1	60	180	120 (66)	20	14	6 (30)	Active
10	F	36	5	180	>300	121 (40)	12	<4	9 (75)	Cure
11	M	62	1.5	60	>300	241 (80)	10	<4	7 (70)	Active
12	F	40	2	300	>300	1 (0)	4	<4	1 (25)	Active
13	M	53	3	180	210	30 (14)	14	10	4 (29)	Active
14	M	40	10	210	>300	81 (27)	20	<4	17 (85)	Cure
15	F	34	2	60	60	0 (0)	26	24	2 (7)	Active
16	F	28	8	120	>300	181 (60)	10	<4	7 (70)	Cure
17	M	40	1.5	180	>300	121 (40)	12	<4	9 (75)	Cure
18	F	61	5	240	>300	61 (20)	8	< 4	7 (62)	Cure
19	M	45	3	120	>300	181 (60)	14	< 4	11 (78)	Cure

Figure 1. A proposed algorithm of managment and treatment of acquired cold urticaria is presented.



DISCUSSION

The management of typical cold urticaria is based on the avoidance of triggering factors, such as cold liquids, air or solids. For symptom control non-sedating H1 antihistamines are recommended.[8] The availability to know the temperature and/or time thresholds by performing provocation test with TempTest® (Emo Systems, GmbH, Berlin, Germany) allows us to objectively **monitor the severity and activity of disease**. Moreover, **it can help patients to better recognize and control cold exposure in their daily lives.** Two previous studies showed a decrease of the CTT measured with the Temp Test that correlated well with the clinical improvement of the acquired cold urticarial activity after a therapeutic intervention[5,9]. We could demonstrate similar results compared with the others previously published. However, the difference from other assays is that our therapeutic intervention was continuous and longer (20 mg of rupatadine daily dose for one year). To our knowledge there is no other study with such long intervention. Two patients did not accepted to be treated continuously and they took rupatadine only on demand. These patients did not clinically improve and the CsTT and CTT did not change from baseline. An elongation of CsTT and a reduction of CTT were observed in the remainder group. Limitations of this study are cohort size and the absence of a control group. But the results of this therapeutic approach can be the basis for further studies that would be suitable to check what is more effective a continuous or an "on-demand" treatment for controlling our cold contact urticarial patients.
There is not still a complete consensus to treat our cold contact urticaria patients. Previous published studies[10-12] consider different non-sedating H1 antihistamines, therapeutic plans and doses. A specific protocol for the management and treatment of cold contact urticaria patients would be necessary for a standardized management. A suggested algorithm is presented.

CONCLUSIONS

Treatment of acquired cold urticaria with daily twenty miligrams of rupatadine for one year demonstrated good outcomes. An improvement of temperature and critical time threshold were detected in all patients that were enrolled to its therapeutic schedule. In most cases an association with a clinical improvement or clinical remission was detected. Herein, we propose an algorithm of management and treatment of patients with acquired cold urticaria.

REFERENCES

1. Magerl M, Borzova E, Giménez-Arnau A, Grattan CEH, Lawlor F, Mathelier-Fusade P, Metz M, Mlynek A, Maurer M. The definition and diagnostic testing of physical and cholinergic urticaries-EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy 2009; 64: 1715-1721.
2. Krause K, Zuberbier T, Maurer M. Modern approaches to the diagnosis and treatment of cold contact urticaria. Curr Allergy Asthm Rep 2010; 10: 243-249.
3. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: recommendationsfor prevention of this complications and a proposal for a diagnostic classification of cold urticaria. J Allergy Clin Immunol 1986; 78: 417-423.
4. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine drecreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: A randomized, placebo-controlled, crossover study. J Allergy Clin Immunol 2009; 123: 672-679.
5. Magerl M, Pisarevskaja D, Staubach P, Martus P, Church MK, Maurer M. Critical temperature threshold measurement for cold urticarial:a randomized controlled trial of H1-antihistamine dose escalation. Br J Dermatol 2012; 166: 1095-1099.
6. Di Leo E, Nettis E, Cassano N, Foti C, Delle Done P, Vena GA, Vacca A. Treatment of acquired cold urticaria with rupatadine. Allergy 2009; 64: 1384-1392.
7. Metz M, Scholz E, Med C, Ferrán M, Izquierdo I, Gimenez-Arnau A, Maurer M. Rupatadine and its effect on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria. Ann Allergy Asthma Immunol 2010; 104: 86-92.
8. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, Grattan CEH, Kapp A, Maurer M, Merk HF, Rogala B, Saini S, Sánchez-Borges M, Schmid-Grendelmeier P, Schünemann H, Staubach P, Vena GA, Wedi B.EAACI /GA2LEN/EDF/WAO guideline: management of urticarial. Allergy 2009; 64:1427-1443.
9. Mlynek A, Magerl M, Siebenhaar F, Weller K, Vieira dos Santos R, Zuberbier T, Zalewska-Janowska A, Maurer M. Results and relevance of critical temperature threshold testing in patients with acquired cold urticaria. Br J Dermatol 2010; 162: 198-200.
10. Magerl M, Schmolke J, Siebenhaar F, Zuberbier T, Metz M, Maurer M. Acquired cold urticaria symptoms can be safely prevented by ebastine. Allergy 2007; 62: 1465-1468.
11. Kaplan A, Treatment of cold urticaria. Curr Allergy Asthma Rep 2010; 10: 223-224.
12. Juhlin L, Vos C, Rihoux JP. Inhibiting effect of cetirizine on histamine-induced and 48/80-induced wheals, and cold-induced urticaria. J Allerg Clin Immunol 1987; 80: 599-602.

Hospital del Mar
Parc de Salut MAR Barcelona