

REVIEW ARTICLE

Cold-induced Anaphylaxis: The Case of a 9-year-old Child and Review of the Literature

Paolo Romita^{a,*}, Paola Mascia^a, Gianfranco Calogiuri^b and Caterina Foti^a

^aDepartment of Biomedical Science and Human Oncology, Dermatological Clinic, University of Bari, Italy; ^bIV Department of Pneumology and Allergy, Civil Hospital Sacro Cuore, Gallipoli (Lecce), Italy

ARTICLE HISTORY

Received: February 22, 2017
Revised: May 11, 2017
Accepted: June 01, 2017

DOI:
10.2174/1871530317666170703122939

Abstract: Background and Objective: The present review investigated cold-induced anaphylaxis, a potentially life-threatening condition that occurs after exposure to cold stimuli and is characterized by respiratory distress and/or hypotension. Anaphylaxis is rarely associated to cold-induced urticarial (CU), a particular form of physical urticaria that is difficult to diagnose and manage. The incidence of cold-induced urticaria has been estimated at about 0.05%, higher in colder regions and in women; its pathological mechanisms are still unknown.

Methods: The literature was searched via the Medline/PubMed database (<http://www.ncbi.nlm.gov/pubmed>).

Results and Conclusion: Patients affected by CU should be well-informed about the risk of anaphylaxis and preventive measures. The prevention of CU is based on the avoidance of cold exposure. The most effective treatment is antihistamines symptomatic therapy. Anyway, patients should also carry with them an emergency kit containing corticosteroids, antihistamines and an epinephrine injector. Future studies are necessary to determine the CU pathophysiology so to establish a more targeted management of this important and potentially life-threatening condition.

Keywords: Anaphylaxis, angioedema, anti-histamines, cold-induced urticaria, cold water, epinephrine, physical urticaria, urticaria.

1. INTRODUCTION

Cold-induced anaphylaxis is a potentially life-threatening condition in which a severe systemic reaction, including respiratory distress and/or hypotension, occurs after skin and body is exposed to a cold stimulus. Anaphylaxis is a rare and extreme clinical feature of cold-induced urticaria (CU), which can be classified as primary (idiopathic), secondary, atypical and familial CU once the cold has been identified as the triggering agent [1]. Primary CU is the most common type and is diagnosed on the basis of a positive ice cube test (ICT). Secondary CU is less common; the ICT is positive and the complaint may be onset by systemic infections or autoimmune diseases such as cryoglobulinemia, HIV, syphilis, hepatitis, parasites and bacterial infections [2]. Upper respiratory tract, teeth or urogenital infections may also be associated with CU and this could explain why patients may occasionally benefit from a course of antibiotic therapy [3]. Atypical CU generally shows more severe clinical manifestations, and the ICT is negative. Familial syndromes are characterized by an earlier onset and the involvement of other systems. They include the Muckle-Wells syndrome, delayed

cold urticaria with autosomal dominant inheritance, rare cases of phospholipase C γ -2 gene mutations and mutations in the cold-induced auto-inflammatory syndrome-1 gene resulting in a cryopyrin-associated periodic syndrome (CAPS) [4-6].

CU is a form of physical urticaria commoner in young adults, but many cases have been reported in the pediatric population, too [7, 8]. The incidence has been estimated at about 0.05%, twice in women, while the frequency ranges between 5.2% and 33.8%, with a higher incidence in colder regions [9, 10]. The disease can last as long as 4-5 years, with improvements or remission of the symptoms in 50% of cases within 5 years. The pathological mechanisms underlying CU, as in other allergic diseases, are still not clear. Mast cells may play an important role, releasing histamine, prostaglandins, leukotrienes and other mediators [11].

2. CASE REPORT

A 9-year-old girl came to our Dermatological Department with her parents, reporting a clinical history of 2 episodes of anaphylactic symptoms after brief contact with cold sea water. The first episode occurred during the first week of June 2014 while the patient was walking in sea water: she suddenly felt a warm sensation spreading over her entire

*Address correspondence to this author at the Department of Biomedical Science and Human Oncology, Dermatological Clinic, University of Bari, Italy; Tel: ?????????????; E-mail: romitapaolo@gmail.com

body with the rapid onset of a generalized urticarial with large wheals spreading from her lower legs to the lower part of her trunk, associated to a dry throat, dyspnea, and loss of consciousness occurred within a few minutes. The child was immediately transported to the local emergency department where clinicians found low blood pressure (80/60mmHg) and a hyperemic throat at the clinical examination. Laboratory tests showed no abnormalities. The patient improved slowly. She denied any recurrences during that summer avoiding further contacts with sea water. The second episode occurred 1 year later, always in June, as soon as she tried to walk again in sea water with the onset of large wheals mainly localized to her lower legs: that time she did not comply loss of consciousness. After the second episode, her medical practitioner sent the girl to our examination for dermatological and allergological evaluation.

The child had no relevant past medical history and her family history was unremarkable. She did not report any similar episodes after the ingestion of cold drinks or during the shower that she used to have with warm/hot water. After obtaining written consent, the ICT was performed at our Department. A plastic bag filled with ice cubes was placed on the volar surface of the patient's forearm for 10 minutes. A giant wheal (Fig. 1) appeared within 3 minutes after removal of the cold plastic bag. Skin prick tests for food allergens were negative, whereas respiratory allergens showed a slight positive response to the *Dermatophagoides* species (house dust mite).

The patient avoided further contacts with cold sea water without any recurrence. In addition, considering her previous anaphylactic reactions, she was prescribed an epinephrine auto-injector pen to be kept available in case of need.

3. DISCUSSION

CU is a chronic physical urticaria that can be difficult to diagnose and manage. Physical Urticaria accounts for about 25% of all cases of chronic urticaria, and from 6 to 34% of patients with physical urticaria have CU [12]. CU can range from mild, localized to diffuse urticaria, angio-oedema and occasionally anaphylaxis secondary to exposure to cold



Fig. (1). A giant wheal appeared within 3 minutes after removal of the cold plastic bag.

stimulus (a cold environment, cold food and liquids ingestion, handling cold objects). Physical signs and the ICT are usually sufficient to diagnose CU.

According to the severity of symptoms, CU can be classified as type 1 localized urticaria and/or angioedema with no respiratory symptoms, type 2 generalized urticaria and/or angioedema with no respiratory symptoms and a type 3 systemic reaction with one episode of respiratory distress (wheezing, short breath) or hypotension [13]. Its most common clinical manifestations are generalized urticaria, dry throat, respiratory distress (wheezing, short breath, dyspnea), hypotension and loss of consciousness.

In our case a 9-year-old girl had 2 episodes of CU after short contact with cold sea water during the summer time. These episodes occurred after few minutes while slowly walking through cold sea water. Rapid onset of generalized urticaria, dry throat, and loss of consciousness for few minutes followed. Diagnosis was performed with ICT. The patient was treated with cetirizine daily with a good response and she was prescribed an epinephrine auto-injector pen to have it available any time if necessary.

Siebenhaar F *et al.* [13] noticed that ICT seems to be an inverse relationship between the minimum time of cold stimulation to induce a confluent wheal (CSTT) and clinical severity of symptoms with hypotensive episodes, mostly with less than 3 minutes rewarming. Instead there is a good correlation with the increasing CSTT and a future improving tolerance to cold stimulation [1]. A review analyzed 30 children with CU in a three-year observation study; it was found that 36.7% of patients developed a type 3 reaction and most of them suffered a decreased level of consciousness (dizziness, fainting, disorientation and shock) more frequently than respiratory distress. In type 3 reactions the main triggers were aquatic activities. The same group was found to have a higher prevalence of atopy and there was no predictive factor for anaphylaxis [14]. A case of a 9-year-old girl who developed cold-induced anaphylaxis while swimming in cold water was recently described. The girl had a history of multiple episodes of cold urticaria in the previous 2 years, but no family history of CU [15]. It is interesting to note that in literature [16-18] more exercise-induced anaphylaxis (EIA) cases have been reported than CU-induced anaphylaxis, which is certainly an uncommon reaction. Food and drug ingestion are the most common factors associated with EIA [16]. EIA is also related to heat [18], while in an epidemiological study of 199 patients with an EIA diagnosis, cold was detected as a determining cofactor in developing EIA in 23% of patients [19]. In one case report only the combination of physical exercise and cold stimulation elicited an anaphylactic reaction in a 16-year-old Japanese boy with an EIA diagnosis [20].

The pathogenesis of cold induced urticaria/anaphylaxis is still unclear, but a serum factor (probably an IgM) seems to play an important role as suggested by different authors [21, 22]. Interestingly cold agglutinins responsible for cold induced hemolytic anemia belong mainly to IgM and IgG subclasses, but IgM are the most harmful autoantibodies, able to cause severe forms of autoimmune hemolytic anemia [23]. Being pentamers, IgM are the most efficient immunoglobulins activating the complement, thus cold induced urti-

caria/anaphylaxis could be mediated by complement activation. Alternatively, it has been proposed that, in cold induced urticaria, IgM (or IgG) may be directed towards surface antigens of platelets as well as in cold induced hemolytic anemia, IgM and IgG are directed towards surface antigens of erythrocytes, thus cold induced urticaria/anaphylaxis could share the same pathomechanism of cold induced hemolytic anemia, but the target cells might be the platelets. Wasserman and Ginsberg have found increased levels of Platelet Factor 4 in 5 patients with cold urticaria challenged by a cold water exposure test [24], suggesting a possible key role of platelets in that physical urticaria. Thus, the complement activation due by the IgM interaction with platelets triggered by cold temperature may lead to platelets destruction with release of vasoactive factors as Platelet Activating Factor (PAF), which is responsible for IgG induced anaphylaxis in mouse [25] and recently it has been demonstrated PAF is able to be the mediator of IgG induced anaphylaxis in humans too [26]. Yet, it is possible cold induced urticaria/anaphylaxis may recognize different pathomechanisms, including an IgE mediated. In this model specific IgE antibodies are directed towards an auto-allergen, probably a not yet identified self-protein whereas cold temperature may induce conformational changes in the tertiary or quaternary structure of that self-protein, leading to the exposure of allergenic epitopes to the interaction with a specific IgE.

When a CU diagnose is performed it is necessary to rule out differential diagnosis. These include allergic reactions (food, drugs, bug bites), aquagenic urticaria [27], other kind of physical urticaria, viral or bacterial induced urticaria [12]. In cases of loss of consciousness during the first year of life another possible cause that should be considered is Dravet syndrome, a rare but severe epilepsy with onset in the early childhood induced by cold stimuli [28].

The prevention of acquired CU is based on the avoidance of cold stimuli owing to the high risk of fatal events. Patients should be properly informed about how to avoid dangerous cold exposure (e.g. chilling, swimming in water under the patient's previously determined individual critical temperature threshold) [29]. The most effective treatment of acquired CU is antihistamines symptomatic therapy so as to prevent pruritus and skin reactions after cold exposure. In some cases high doses of anti-histamines are required, the recommended dose being up to four times daily, whereas patients often receive only low dose treatments [30]. This is an important aspect because of the poor quality of life of these patients and the risk of developing life-threatening complications after eating cold foods or during aquatic activities. For these reasons, further studies are necessary to establish the appropriate anti-histamine treatment regimens, and other therapeutic options should be considered like the concomitant use of cyclosporin [31], corticosteroids [32], anti-IgE [33], and leukotriene antagonists [34] in high-risk acquired CU. Antibiotic treatments have been described to induce remission in small case series and in case reports [3, 35]. In particular Doxycycline demonstrated its immune regulatory activity and its impact on cytokine production down-regulating TNF- α , IL1- β and IL6 involved in inflammatory skin disorders [3, 36]. Omalizumab, a recombinant humanized monoclonal anti IgE antibody, has recently been approved as an add-on therapy for refractory chronic spontaneous urti-

caria (300mg per month). In a case series significant improvement in respect to quality of life after 5 months of treatment with omalizumab was observed [37].

Patients with severe symptoms of acquired CU or with a high risk of developing anaphylactic reactions should be equipped with an emergency kit containing corticosteroids, antihistamines and an epinephrine injector. Cold tolerance induction is an effective method of treating patients with acquired CU, but it needs to be done under medical supervision because of the risk of systemic reactions [38].

CONCLUSION

Patients affected by CU should be well-informed about the risk of anaphylaxis and preventive measures. They have to avoid rapid exposure to cold water and should be managed by preventing episodes using prophylactic second generation anti-histamines, carrying an epinephrine auto-injection pen and using it if necessary. Future studies are necessary to determine the CU pathophysiology so to establish a more targeted management of this important and potentially life-threatening condition.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

All the authors have contributed substantially to the design, performance and analysis of the work.

REFERENCES

- [1] Wanderer, A.A. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis and management. *J. Allergy Clin. Immunol.*, **1990**, *85*, 965-981.
- [2] Yu, G.W.A.; Mahmoudi, M. Cold urticaria challenging cases in allergic and immunological diseases of the skin. *BMJ Case Rep.*, **2013**, *2013*, pii: bcr2013010441.
- [3] Gorczyza, M.; Schoepke, N.; Krause, K.; Hawro, T.; Maurer, M. Patients with chronic cold urticaria may benefit from doxycycline therapy. *Br. J. Dermatol.*, **2017**, *176*, 259-261.
- [4] Ombrello, M.J.; Remmers, E.F.; Sun, G.; Freeman, A.F.; Datta, S.; Torabi-Parizi, P.; Subramanian, N.; Bunney, T.D.; Baxendale, R.W.; Martins, M.S.; Romberg, N.; Komarow, H.; Aksentijevich, I.; Kim, H.S.; Ho, J.; Cruse, G.; Jung, M.Y.; Gilfillan, A.M.; Metcalfe, D.D.; Nelson, C.; O'Brien, M.; Wisch, L.; Stone, K.; Douek, D.C.; Gandhi, C.; Wanderer, A.A.; Lee, H.; Nelson, S.F.; Shianna, K.V.; Cirulli, E.T.; Goldstein, D.B.; Long, E.O.; Moir, S.; Meffre, E.; Holland, S.M.; Kastner, D.L.; Katan, M.; Hoffman, H.M.; Milner, J.D. Cold urticaria immunodeficiency and autoimmunity related to PLCG2 deletions. *N. Eng. J. Med.*, **2012**, *366*, 330-338.
- [5] Kolivras, A.; Theunis, A.; Ferster, A.; Lipsker, D.; Sass, U.; Dusart, A.; André, J. Cryopirin-associated periodic syndrome: an auto-inflammatory disease manifested as neutrophilic urticarial dermatosis with additional perieccrine involvement. *J. Cutan. Pathol.*, **2011**, *38*, 202-208.
- [6] Furr, J.C.; Panda, M. Cold-induced urticaria with a familial transmission: a case report and review of the literature. *J. Med. Case Rep.*, **2012**, *6*, 70.

- [7] Neittaanmäki, H. Cold urticaria: clinical findings in 220 patients. *J. Am. Acad. Dermatol.*, **1985**, *13*, 636-644.
- [8] Ting, S. Cold-induced urticaria in infancy. *Pediatrics*, **1984**, *73*, 105-106.
- [9] Moller, A.; Henning, M.; Zuberbier, T.; Czarnetzki-Henz, B.M. Epidemiology and clinical aspects of cold urticaria. *Hautarzt* **1996**, *47*, 510-514.
- [10] Moller, A.; Henz, B.M. Cold Urticaria. In: Zuberbier T, Ed. *Urticaria: clinical, diagnostic and therapeutic aspects*. Berlin: Springer **1998**.
- [11] Bochner, B.S.; Lichtenstein, L.M. Anaphylaxis. *N. Engl. J. Med.*, **1991**, *324*, 1785-1790.
- [12] Abajian, M.; Mlynec, A.; Maurer, M. Physical Urticaria. *Curr. Allergy Asthma Rep.*, **2012**, *12*, 281-287.
- [13] Wanderer, A.A.; Hoffman, H.M. The spectrum of acquired and familial cold induced urticaria/urticaria like syndromes. *Immunol. Allergy Clin. North Am.*, **2004**, *24*, 259-286.
- [14] Alangari, A.A.; Twarog, F.J.; Shih, M.C.; Schneider, L.C. Clinical feature and anaphylaxis in children with cold urticaria. *Pediatrics*, **2004**, *113*, e313-e317.
- [15] Fernando, S.L. Cold-induced anaphylaxis. *J. Pediatr.*, **2009**, *154*, 148-148.e1.
- [16] Castells, M.C.; Horan, R.F.; Sheffer, A.L. Exercise-induced anaphylaxis. *Clin. Rev. Allergy Immunol.*, **1999**, *17*, 413-424.
- [17] Jaqua, N.T.; Peterson, M.R.; Davis, K.L. Exercise-Induced Anaphylaxis: A Case Report and Review of the Diagnosis and Treatment of a Rare but Potentially Life-Threatening Syndrome. *Case Rep. Med.*, **2013**, *2013*, 610726.
- [18] Black, A.K.; Champion, R.H. Physical and cholinergic urticarias. In: Champion, R.H.; Eds. *Textbook of dermatology Volume 3* 6th edition. Oxford: Blackwell Science **1998**, pp. 2128-2134.
- [19] Wade, J.P.; Liang, M.H.; Sheffer, A.L. Exercise-induced anaphylaxis: epidemiologic observations. *Prog. Clin. Biol. Res.*, **1989**, *297*, 175-182.
- [20] Ii, M.; Sayama, K.; Tohyama, M.; Hashimoto, K. A case of cold dependent exercise- induced anaphylaxis. *Br. J. Dermatol.*, **2002**, *147*, 368-370.
- [21] Inoue, S.; Teshima, G.; Ago, Y.; Nagata, S. Cold urticaria associated with immunoglobulin M serum factor. *J. Allergy Clin. Immunol.*, **1980**, *66*, 299-304.
- [22] Wanderer, A.A.; Maselli, R.; Ellis, E.F.; Ishizaka, K. Immunologic characterization of serum factors responsible for cold urticaria. *J. Allergy Clin. Immunol.*, **1971**, *48*, 13-22.
- [23] Barcellini, W. New insights in the pathogenesis of autoimmune hemolytic anemia. *Transfus. Med. Hemother.*, **2015**, *42*, 287-293.
- [24] Wasserman, S.I.; Ginsberg, M.H. Release of platelet factor 4 into the blood after cold challenge of patients with cold urticaria. *J. Allergy Clin. Immunol.*, **1984**, *74*, 275-279.
- [25] Finkelman, F.D. Anaphylaxis: lessons from mouse models. *J. Allergy Clin Immunol.*, **2007**, *120*, 506-515.
- [26] Muñoz-Cano, R.; Picado, C.; Valero, A.; Bartra, J. Mechanisms of anaphylaxis beyond IgE. *J. Investig. Allergol. Clin. Immunol.*, **2016**, *26*, 73-82.
- [27] Rothbaum, R.; McGee, J.S. Aquagenic urticaria: diagnostic and management challenges. *J. Asthma Allergy*, **2016**, *9*, 209-213.
- [28] Verbeek, N.E.; Wassenaar, M.; van Campen, J.S.; Sonsma, A.; Gunning, B.; Knoers, N.; Lindhout, D.; Jansen, F.E.; Leijten, F.; Brilstra, E.H.; Kasteleijn-Nolst Trenité, D. Seizure precipitants in Dravet syndrome: What events and activities are specifically provocative compared with other epilepsies? *Epilepsy Behav.*, **2015**, *47*, 39-44.
- [29] Zuberbier, T.; Asero, R.; Bindslev-Jensen, C.; Walter Canonica, G.; Church, M.K.; Giménez-Arnau, A.M.; Grattan, C.E.; Kapp, A.; Maurer, M.; Merk, H.F.; Rogala, B.; Saini, S.; Sánchez-Borges, M.; Schmid-Grendelmeier, P.; Schünemann, H.; Staubach, P.; Vena, G.A.; Wedi, B. Dermatology Section of the European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticarial. *Allergy*, **2009**, *64*, 1427-1443.
- [30] Siebenhaar F, Staubach P, Mets M, Magerl, M.; Jung, J.; Maurer, M. Peltier effect-based temperature challenge- an improved method for diagnosing cold urticaria. *J. Aallergy Clin. Immunol.*, **2004**, *114*, 1224-1225.
- [31] Marsland, A.M.; Beck, M.H. Cold urticaria responding to systemic ciclosporin. *Br. J. Dermatol.*, **2003**, *149*, 214-215.
- [32] Black, A.K.; Eady, R.A.; Greaves, M.W.; Keahey, T.M.; Sibbald, G. Treatment of acquired cold urticaria by prednisone: dissociation of histamine release and clinical improvement. *Br. J. Clin. Pharmacol.*, **1980**, *9*, 116P-117P.
- [33] Boyce, J.A. Successful treatment of cold induced urticaria anaphylaxis with anti IgE. *J. Allergy Clin. Immunol.*, **2006**, *117*, 1415-1418.
- [34] Bonadonna, P.; Lombardi, C.; Senna, G.; Canonica, G.W.; Passalacqua, G. Treatment of acquired cold urticaria with cetirizine and zafirlukast in combination. *J. Am. Acad. Dermatol.*, **2003**, *149*, 214-215.
- [35] Buss, Y.L.; Sticherling, M. Cold Urticaria: disease course and outcome – an investigation of 85 patients before and after therapy. *Br. J. Dermatol.*, **2005**, *153*, 440-441.
- [36] Di Caprio, R.; Lembo, S.; Di Costanzo, L.; balato, A.; Monfrecola, G. Anti-inflammatory properties of low and high doxycycline doses: an *in vitro* study. *Mediators Inflamm.*, **2015**, *2015*, 329418.
- [37] Kitsioulis, N.A.; Xepapadaki, P.; Kostoudi, S.; Manousakis, E.; Douladiris, N.; Papadopoulos, N.G. Omalizumab in pediatric cold contact urticaria: warm blanket for a cold bath. *Pediatr. Allergy Immunol.*, **2016**, *27*, 749-764.
- [38] Black, A.K.; Sibbald, R.G.; Greaves, M.W. Cold urticaria treated by induction of tolerance. *Lancet*, **1979**, *2*, 964.