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Omalizumab in Pediatric Cold Contact Urticaria: Warm Blanket for a Cold Bath?

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To the editor

Cold urticaria, or cold contact urticaria (CCU), is a subtype of physical urticaria presenting with pruritic wheals (hives) and/or angioedema or even anaphylaxis following contact with cold objects, liquids or cold air (1). CCU most often occurs during or after water immersion, potentially resulting in life-threatening events, either due to systemic anaphylactic reaction or drowning. Most affected patients are young adults, with a reported incidence of 0.05% in Central Europe, although anecdotal data are suggestive of increased incidence in Southern European countries, due to regular sea contact (2). The underlying pathophysiology is largely unknown; nevertheless, activation of cutaneous mast cells and subsequent release of pro-inflammatory mediators following cold exposure plays an important role. Diagnosis is based on the 'ice cube test' (ICT), which consists of

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the application of an ice cube on the skin of the forearm for pre-specified time intervals (usually 1, 3, 5 and 10 minutes). A positive test is characterized by induction of urticarial skin lesions at the cold challenge during the observation time (usually 5 minutes). A more sophisticated and standardized diagnostic test (TempTest) has been introduced for determination and monitoring of the threshold temperatures that induce CCU patients' symptoms (3). Antihistamines are the treatment of choice in the treatment of CCU, while increased doses up to fourfold have been recommended in case of persistence, in line with chronic urticarial guidelines (3).

Omalizumab, a recombinant humanized monoclonal anti – IgE antibody, has recently been approved as an add-on treatment for refractory chronic spontaneous urticaria in adults and children older than 12 years of age (4).

Although a limited number of reports supports a potential beneficial effect of omalizumab in adults with CCU, similar data in adolescents and children are lacking.

We present herein a case series of adolescents with refractory CCU in which omalizumab was used as an add-on treatment.

Patients and methods

We include in this report 5 adolescents with CCU, all females, mean aged 14.6 years (SD = 0.65, range 14 – 15.5 years), who were treated with omalizumab (300 mg/month), due to either non-responsiveness or severe adverse effects (somnolence, anxiousness, reduction in school attribution) to antihistamines.

In order to exclude underlying causes of CCU the following work-up was performed at baseline: complete blood count, CRP, ESR, glucose, urea, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), serum iron, ferritin, ASTO, C4, Ra test, cryoglobulins, cold agglutinins, thyroid evaluation (TSH, T3, fT4, anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies), IgM and IgG antibodies to Epstein-Barr virus, antibodies to hepatitis B and C and total IgE.

A baseline ICT was conducted to all patients. Antihistamines were withheld for seven days prior to testing. Re-assessment was performed on a monthly basis, post-initiation of treatment with omalizumab, in the context of clinical follow-up of the patients.

Accepted Article

Patients' quality of life was assessed by the Children's Dermatology Life Quality Index (CDLQI) at baseline and at one and five months, post-initiation of omalizumab. CDLQI is a validated 10-item questionnaire including leisure, symptoms, emotional effects, personal relationships, quality of sleep, school attribution or holiday-enjoyment and skin-treatment. It is self-explanatory and can be simply handed to the patient who is asked to fill it in with the help of the child's parent or guardian. The scoring of each question refers to disturbance and ranges from 0 (not at all) to 3 (very much). Scoring is graded as very much (3 points), quite a lot (2 points), only a little (1 point), and not at all (0 points). The CDLQI is calculated by summing the score of each question resulting in a potential range of 0-30. The higher the score, the more the quality of life is impaired (5).

All 5 patients reported their first episode of CCU during sea-swimming. Four of them (patients 1, 3, 4, 5) experienced an anaphylactic reaction (2 with dizziness, urticarial rash and repetitive vomiting and 2 other with generalized urticarial rash and a confirmed drop in blood pressure), while one patient (patient 2) reported having a mild reaction (generalized urticaria). All patients were treated with second generation antihistamines, following their first episode. However, they had further episodes, mainly urticaria following exposure to cold air/water and local edema after contact with cold objects.

Due to the fact that episodes of CCU were resistant (further reported episodes during exposure to cold) to single dose administration of H1-antihistamines we decided quadrupling the dose in 3 out of 5 patients, (two on levocetirizine 5 mg and one on desloratadine 5mg), while the remaining 2 patients received tripled doses (one on levocetirizine 5 mg and one on desloratadine 5 mg). During treatment 2 patients -patients 4, 5- reported antihistamine-related adverse side effects which affected their daily routine (somnolence, reduction in school attribution, anxiousness).

Due to either patients' unresponsiveness to antihistamine treatment or severe side effects, patients were prescribed omalizumab (300 mg per month) (6).

Results - Discussion

The mean age of patients' reported first CCU episode was 11 years (SD = 2.71, range 7 – 13.5 years). The mean range of total IgE levels were 700.62 IU/ML (4 – 2415 IU/ML). In respect to personal medical history two of them (patient 4, 5) reported a history of atopic dermatitis and patient 1 had active allergic rhinitis. Interestingly, one patient's father had a positive history of CCU during adolescence.

Investigation for underlying pathologies were negative, while ICTs were positive in all cases (3 patients had positive ICT at 1 min, while the other 2 patients at 3 and 5 min respectively).

All patients reported significant improvement in respect to quality of life, corresponding to a decrease of score of CDLQI by 41.46% (13.4% - 65.3%, SD = 18.66) after 5 months of treatment with omalizumab. In 4 out of 5 patients, improvement was observed just after the first month of treatment (decrease range 17.65% - 40%, SD = 10.35) (Figure 1).

Longitudinal assessment of both CDLQI and ICT is shown at Table 1.

In respect to ICT, significant reductions in reaction time needed to elicit a wheal response were noted in all children (Figure 2). Three children resulted with negative ICT within a period of five months. The earliest negative response was noted for case 4 at 2 months, while in 2 children a prolongation of four minutes was recorded.

All patients reduced the needed dose of antihistamines (3 discontinued and 2 used occasionally), with subsequent reduction of reported side effects.

In respect to omalizumab, only local side effects were noted, such as minimal local bleeding, localized swelling and discomfort due to the injection procedure, in 2 patients of the study. No other side effects were reported.

In our study we observed that most of our patients' episodes were reported during sea swimming. This is consistent with references to previous studies (2). This fact possibly explains the increased episodes of CCU in the Southern European countries and especially those surrounded by Mediterranean Sea, in comparison with countries of the Northern Europe. In a previous study from our group (7), concerning the pattern of incidence of childhood acute urticaria between Northern (Norwich) and Southern (Heraklion) Europe, a statistically significant correlation of episodes of acute urticaria were observed only in relevance with respiratory infections, between 2 cities with similar characteristics. However, as shown in the study, there was a higher incidence of urticaria episodes at Heraklion during the period of July to September. Taking into consideration that the implication of respiratory infections is low during spring months, as stated by the authors, a possible explanation for that differentiation in the incidence of the episodes could conceivably be an increase of episodes of CCU following swimming.

Since potentially life-threatening events might result from CCU, all patients were provided with a detailed written action plan, including adrenaline auto injector, with appropriate training in its use. Surprisingly none of the patients reported use of adrenaline prior to omalizumab introduction.

To our knowledge, this is the first case series, supporting a possible role of omalizumab as an add-on therapy in refractory CCU in children. The choice of omalizumab as treatment option in refractory CCU contributed greatly both to efficiently control disease symptoms and also improve quality of life of our patients.

Although other tests have been also suggested in the management of patients with ICU, such as TempTest, providing potentially a more accurate determination of temperature thresholds for symptoms induction (3), we only used ICT test, due to availability. There are only a few case reports on the use of omalizumab for CCU in children. The time - response either for ICT or CDLQI improvements, was comparable with reported cases (6) although only a dose of 75 mg on a monthly basis was used in these reports. Levels of IgE as measured at baseline were not indicative of the response in accordance with previous reports (8). Our results, concerning the positive effect of omalizumab in CCU, coincide with Sussman et al, even though it is not quite clear if the therapeutic intervention in their study referred to adult patients or children. In contrast to the studies of Metz et al (8) and Le Moing et al (9), including adult patients, we didn't observe recurrence of patients' symptoms neither during administration of omalizumab nor after cessation of treatment. Although various case reports (10) described adult CCU patients with low responsiveness to omalizumab, this was not the case in our younger patients. Our patients were given a dose of 300 mg of omalizumab, even though Metz et al described respective good response to 1 patient of similar age (19 years) after the administration of a lower dose (150 mg)(8).

Although the pathogenesis of CCU is largely unclear, it has been postulated that either specific IgE antibodies react against specific skin antigens (possibly autoantigens) at the appropriate temperature or circulating IgG (or IgM) autoantibodies act against either IgE or its high-affinity receptor (FcεRI) on cutaneous mast cells, thus leading in release of histamine and other inflammatory mediators, providing a potential mechanism by which omalizumab acts in CCU patients.

Two out of 5 patients discontinued treatment with omalizumab after 5 and 11 months respectively (patients 3 and 4). Two patients still receive omalizumab 300 mg/monthly (patients 2 and 5 / duration of treatment with omalizumab 13 and 11 months respectively), while one patient (patient 1) is receiving omalizumab 300 mg/month since last year but only for a time period of 4 months/year

(June – September) corresponding to the summer period in Greece, and based on positive ICT result and patient's preference. Among patients that are still on treatment with omalizumab, patient 2 mentioned palm erythema upon contact with frozen foods without experiencing other symptoms during swimming or exposure to cold air, while patients 1 and 5 didn't report any symptoms. Furthermore only patient 1 reported sporadic use of H1- antihistamine (bilastine 20 mg – before sea swimming), while the other 2 did not report concomitant use of H1-antihistamines. None of the patients that discontinued treatment with omalizumab reported symptom relapse; one has sporadically used a H1-antihistamine (bilastine 20 mg) during swimming as a precaution.

We intent to prospectively follow-up each patient, in order to assess the clinical course and detect possible relapse following omalizumab discontinuation. Larger cohorts comparing omalizumab either with placebo or other medications proposed by EAACI guidelines as add-on treatments in chronic urticaria are needed. Response to omalizumab at 300mg in adolescents with refractory CCU, both in terms of efficacy and safety, taken together with the notion that the disease may have similar mechanisms in younger patients, suggests the need for performing additional studies to expand the age range for use of this treatment.

Figure 1. CDLQI following treatment with omalizumab

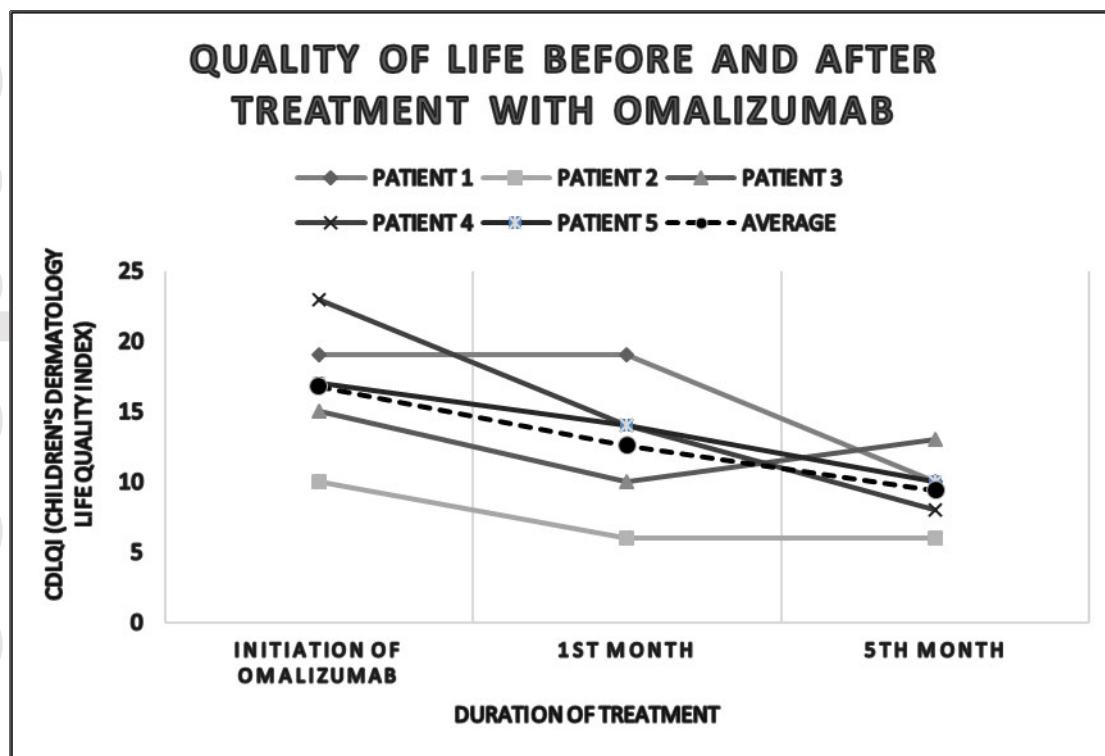
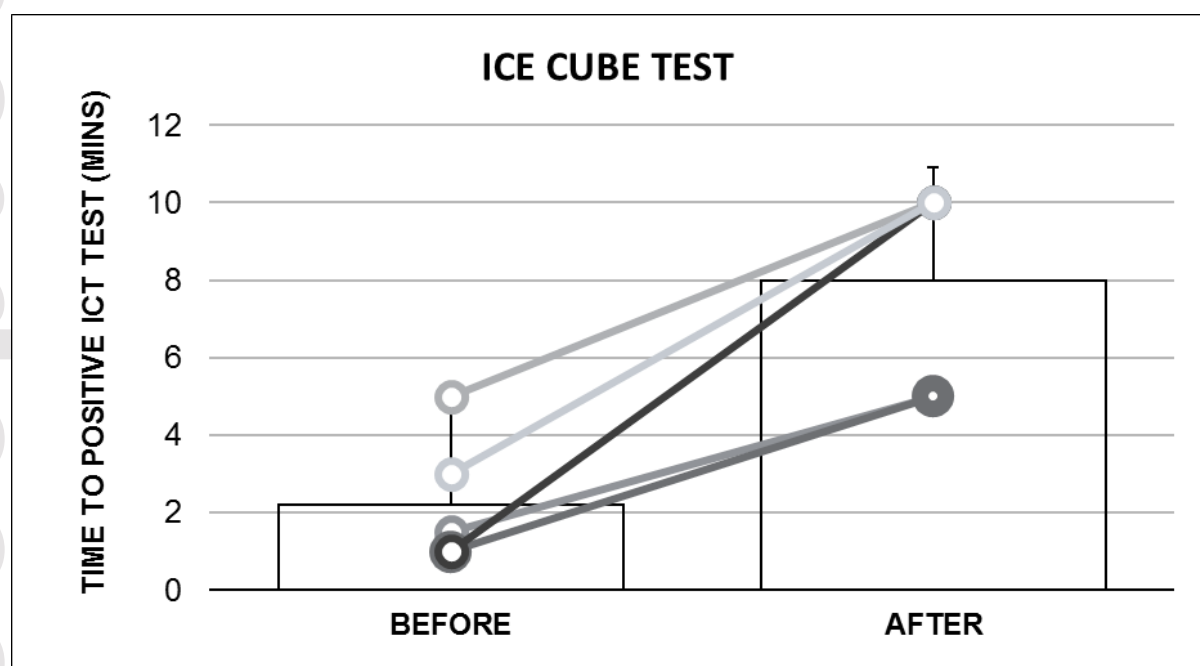


Table 1. Longitudinal follow-up of ice cube challenge test and CDLQI

Patients	Positivity of ICT before omalizumab (min)	Positivity of ICT after omalizumab (min)	Time to ICT negativity post omalizumab (months)	CDLQI before omalizumab	CDLQI at 1month post omalizumab initiation (score, % reduction)	CDLQI at 5months post omalizumab initiation (score, % reduction)
P 1	1	5	Still positive	19	19 (0)	10 (47.4)
P 2	5	Negative	5	10	6 (40)	6 (40)
P 3	1	5	Still positive	15	10 (33.33)	13 (13.4)
P 4	1	Negative	2	23	14 (39.13)	8 (65.3)
P 5	3	Negative	2,5	17	14 (17.65)	10 (41.2)

Figure 2. Ice cube test change before and 5 months after omalizumab treatment in adolescents with refractory CCU (ICT was considered negative if no wheal response was noted in more ≥ 10 minutes).



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