

ORIGINAL ARTICLE

Cold urticaria: a 20-year follow-up study

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Abstract

Background Chronic cold urticaria results in significant morbidity, yet information on its natural history is limited.**Objective** We examined the natural history of chronic cold urticaria and its impact on quality of life.**Methods** We analysed the characteristics of patients diagnosed with cold urticaria at a community-based specialist allergy practice in the Australian Capital Territory (ACT) between 1995 and 2015. Follow-up data were obtained using a mailed questionnaire. Possible predictive factors of disease severity and symptom duration were evaluated.**Results** A total of 99 patients were assessed with a median age of 42 (range 5–81 years); 63% were female and the median age of onset of symptoms was 22 years. Of 41 questionnaire responders (14 ± 10.9 years follow-up; median 12 years), 5- and 10-year resolution rates were 17.9% ± 6.2% and 24.5% ± 7.2%, respectively. Whereas 22% reported resolution and 23% described improvement, the remaining 55% reported stable or worsening disease. Most individuals relied on lifestyle modification to ameliorate symptoms rather than medication. Risk factors for persistent disease were intercurrent atopic disease ($P = 0.025$) and those with longer duration of symptoms at the time of initial assessment ($P < 0.001$). Secondary causes of cold urticaria were identified in only two patients, both with B-cell malignancy.**Conclusion** In a subset of patients, cold urticaria has low rates of spontaneous resolution and results in lifestyle changes and impaired quality of life.

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Conflicts of interest

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Introduction

First described in the 1860s, cold urticaria is one of the most common forms of physical urticaria. Onset is most common in early adult life, is more common in females and, perhaps unsurprisingly, higher rates are reported in cooler climates.^{1–3} Symptoms arise following exposure to cool air, surfaces or water less than body temperature.⁴ Up to a third of individuals experience systemic symptoms such as headache, fatigue or generalised urticaria through to anaphylaxis. Anaphylaxis (including fatalities from drowning) may occur with complete body immersion in cold water while swimming.^{3,5,6} Infusion of cool intravenous solutions and surgical procedures pose a similar risk.^{7,8}

Despite the significant morbidity that may arise from cold urticaria, it has been rarely studied on its own, there is limited information on its natural history or factors predicting prognosis and there are few studies of the effectiveness of treatment in cold urticaria as a specific entity. The primary aim of this study

was to examine the natural history of cold urticaria in a cohort of patients assessed in a specialty allergy practice over 20 years. Data derived from a retrospective chart review were combined with a follow-up patient questionnaire to assess symptom severity and duration, and prognostic factors related to disease duration and severity. Our secondary aims were to examine impact on quality of life, response to treatment and adherence to recommended management.

Materials and methods

Study population

The study was undertaken in a mixed adult/paediatric specialty allergy/immunology private practice in the Australian Capital Territory (ACT) in South-Eastern Australia. The practice serves the local metropolitan population of Canberra (population = 383 000) and surrounding regional areas. The practice

provides approximately half the local ambulatory specialist allergy services, the closest services outside the ACT being Sydney or Melbourne, 300 and 800 km away, respectively. Referrals were received from general medical practitioners, specialist adult physicians, dermatologists and paediatricians. The second author assessed all patients. Clinical and demographic data were entered prospectively into a searchable database (Blue Chip Clinical Research Module, Health Communication Network, Sydney; Microsoft Access, Microsoft Corporation, Redmond, WA, USA). Patients diagnosed with cold urticaria between February 1995 and January 2015 were identified retrospectively from the database. Clinical records were reviewed to confirm the diagnosis of cold urticaria and to extract relevant clinical data. These included demographic data, date of initial consultation, intercurrent atopic disease (asthma, atopic eczema, allergic rhinitis, food or insect sting allergy) and recommendations regarding use of medical alert jewellery or adrenaline auto-injector provision.

Diagnostic criteria

Cold urticaria was defined as previously described,⁴ as the development of urticaria in response to exposure of skin contact with air, surfaces or water less than body temperature. Cold urticaria was classified as localised if urticaria only developed at sites of localised skin cooling. Cold urticaria was classified as generalised if patients either developed urticaria following generalised cold exposure (such as complete body immersion) or developed generalised urticaria after localized cold exposure, however, without dangerous features of anaphylaxis. A diagnosis of anaphylaxis was only assigned if either of the first two criteria of the 2006 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium definition was fulfilled.⁹ Specifically, patients were labelled as having anaphylaxis if their symptoms included respiratory symptoms of noisy or difficulty breathing (dyspnoea, bronchospasm/wheeze, cyanosis/hypoxia) and/or cardiovascular compromise (loss of consciousness or reported presyncope) following exposure to cold. A diagnosis of cold urticaria was based on a combination of history, physical examination and deliberate cold provocation. Questions on history included the development of urticaria or anaphylaxis following exposure to cold environments, ingestion of cold foods and drinks, immersion in cold water or after touching cold objects. The cold provocation test involved applying an ice cube in a plastic bag to the patient's forearm for 5 min, after which the stimulus was removed to allow the skin to return to normal skin temperature. A positive test was defined as the development of a weal response in the 10-min period of skin re-warming.² We did not, however, have access to objective measurements of temperature threshold. Investigations were undertaken to prove or disprove the presence or absence of underlying disease; these included full blood count, electrolytes, blood glucose level, liver

function tests, thyroid function, serum electrophoresis, cold agglutinins and cryoglobulins, infectious disease serology where relevant or other investigations where clinically indicated.

Patient management

Patients were provided with verbal and printed information on the potential causes and treatment options for cold urticaria, including the use of H₁ and H₂ histamine antagonists for the treatment of symptoms or for prophylactic use if cold exposure was anticipated. Patients were evaluated for the presence or absence of previous anaphylaxis or participation in high-risk activities such as water sports, snow sports or camping in remote areas that might increase the risk of inadvertent hypothermia. They were warned about the risk of anaphylaxis with complete body immersion in water and advised to avoid swimming in cold water, to never swim alone, to stay close to shore if swimming in the sea, to premedicate with a combination of H₁ (between 1 and 4 tablets/day¹⁰) and H₂ histamine receptor antagonists and to test the circumstances before swimming. They were advised about potential sources of other intense cold exposure such as surgical operating theatres and to warn surgeons or anaesthetists in advance of planned surgical procedures so that appropriate precautions could be undertaken. Those who had experienced anaphylaxis (or considered at higher risk of future anaphylaxis) were advised to wear medical alert jewellery and carry an adrenaline auto-injector (AAI) to use in an emergency. Patients were advised to return for follow-up if symptoms failed to respond to initial therapy.

Follow-up survey

Patients identified with a diagnosis of cold urticaria were mailed a questionnaire (with stamped addressed reply envelope) in December 2014, with reminders mailed in March 2015 if replies were not received. The questionnaire included queries about symptom frequency and severity, triggers, presence or absence of systemic symptoms (including anaphylaxis), impact on quality of life and activities, use of medical alert identification jewellery and response to medication. Symptom severity was quantified by patients using a visual analogue scale from 0 (absent) to 10 (severe/debilitating). Impact on quality of life was assessed using a scoring system from 0 to 3 corresponding to no impact, occasional impact, frequent impact or impact all of the time, respectively, in the domains of work, leisure and social activities, sport and social embarrassment. Questions assessed the patients' overall experience of disease from the onset of symptoms.

Ethics approval

The Human Research and Ethics Committee (Calvary Bruce/Calvary John James Private Hospitals, Canberra, Australia) approved the study. All questionnaire responders provided informed written consent.

Data analysis

Data were analysed using SPSS Version 20 software (SPSS, Chicago, IL, USA). Quantitative data are presented as mean for normal data or median for non-normal data, or as a table of frequencies for qualitative data. Kaplan–Meier analysis was used to estimate the proportion of patients whose cold urticaria persisted as a function of time. The age when symptoms commenced was taken to represent the start of the analysis. Non-parametric tests (Mann–Whitney *U*-test, Spearman's correlation, Chi-square test for independence) were used in the subsequent analysis to test whether disease duration or disease severity were related, or differed according to four other variables of gender, atopic comorbidity, age of disease onset and preassessment duration of disease. Disease severity was defined as the presence or absence of anaphylaxis as the most objective measure of severity.

Results

Patient characteristics

A total of 99 patients were diagnosed with cold urticaria, of whom 62 were female. Age ranged between 5 and 81 years (median 42). The median age of onset was 22 years (range <1–78 years). Symptoms were provoked most commonly by

exposure to cold water or air. All cases of anaphylaxis followed immersion in cold water (Table 1). Preceding illness was reported by eight patients: respiratory infections ($n = 5$); and one each following EBV infection, ranitidine anaphylaxis or a wasp sting. Two patients were diagnosed with B-cell malignancy (one case each of CLL and lymphoma); one diagnosed with hypothyroidism; one had active *Helicobacter* infection (but treatment did not help cold urticaria); low-titre cold agglutinins were identified in two patients and one patient had detectable cryoglobulins and cryofibrinogen.

Follow-up patient survey

Follow-up survey data were available from 41/99 patients (41.4%; Table 2). No significant differences were observed between responders and non-responders in terms of age, gender, age of onset of symptoms, atopic disease, anaphylaxis or recommendation of medical alert jewellery or adrenaline auto-injector use. Although not all responders answered every question, non-response rates were low (<8%) and tabulated data were adjusted accordingly. Specifically, responses were not received regarding whether symptom severity had changed ($n = 3$), the frequency of symptoms ($n = 1$), symptoms experienced ($n = 2$) or treatments used ($n = 2$).

Table 1 Baseline characteristics of total patient population with cold urticaria

	Questionnaire responders ($n = 41$)	Questionnaire non-responders ($n = 58$)	<i>P</i> -value	Total ($n = 99$)
Female: n (%)	28 (68.3)	34 (58.6)	0.327	62 (62.6)
Age (years): median (range)	35 (5–81)	44 (14–75)	0.250	42 (5–81)
Age of onset (years): median (range)	17 (2–78)	26 (0–61)	0.177	22 (0–78)
Duration of symptoms at initial consultation (years): median (range)	3 (0–49)	1.5 (0–47)	0.923	2 (0–49)
Triggers: n (%)				
Cold water	38 (92.7)	37 (63.8)	0.001*	75 (75.8)
Cold air	35 (85.4)	38 (65.5)	0.036*	71 (71.7)
Cold surfaces	25 (61.0)	13 (22.4)	0.001*	38 (38.4)
Cold food/beverages	14 (34.1)	5 (8.6)	0.002*	19 (19.2)
Anaphylaxis	16 (39.0)	12 (20.7)	0.052	28 (28.3)
Comorbidity: n (%)				
Atopic disease	22 (53.7)	24 (41.4)	0.258	46 (46.5)
Other urticaria				
Cholinergic	11 (26.8)	5 (8.6)	0.015*	16 (16.2)
Dermographism	5 (12.2)	11 (19.0)	0.813	16 (16.2)
Heat	4 (9.8)	4 (6.9)	0.418	8 (8.1)
Spontaneous	1 (2.4)	5 (8.6)	0.395	6 (6.1)
Pressure	2 (4.9)	2 (3.4)	†	4 (4.0)
Vibration	0 (0)	1 (1.7)	†	1 (1.0)
Recommendations (%)				
Medical alert jewellery	7 (17.1)	7 (12.1)	0.504	14 (14.1)
Adrenaline auto-injector	9 (21.9)	12 (20.7)	0.915	21 (21.2)

**P*-value significant at $P < 0.05$ level.

†Numbers too small to be calculated.

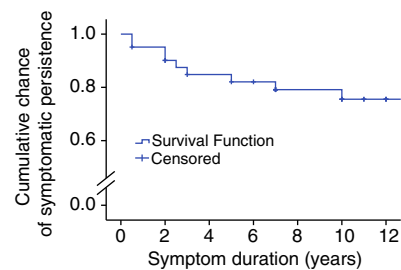
Table 2 Characteristics of questionnaire responders

Patients (n)	41
Symptom duration (years): median (range)*	10 (0.5–50)
Natural History: n (%)	
Resolved	9 (22.0)
Improved	9 (23.1)
Stable	18 (47.4)
Worse	3 (7.9)
Frequency: n (%)	
Most days	9 (29.0)
≥ Weekly	4 (12.9)
Cooler months only	5 (16.1)
Specific conditions (e.g. cold air/water)	15 (48.4)
Symptoms: n (%)	
Urticaria (exposed skin only)	12 (30.7)
Urticaria (including non-exposed skin)	23 (59.0)
Anaphylaxis (ever)	16 (41.0)
Dizziness	5 (12.8)
Dyspnoea	4 (10.3)
Other	11 (28.2)
Recommendations n(%)	
Medical alert jewellery used/advised	3/7 (43)
AAI available/advised	1/9 (11)
Management: n (%)	
H ₁ antihistamines	35 (89.7)
H ₂ antihistamines	3 (7.7)
Lifestyle modification	16 (41.0)
Medication effectiveness score: median (range)	5 (0–10)
Severity score: median (range)	5 (2–10)
Quality-of-life score: mean (range)	
Work	0.54 (0–3)
Leisure	0.95 (0–3)
Sport	0.95 (0–3)
Social activity	0.81 (0–3)
Embarrassment	0.68 (0–3)

*Describes total duration from time of onset to questionnaire reply.
AAI, adrenaline auto-injector.

Follow-up data were available for a total of 508 patient years, corresponding to a mean duration of follow-up of 14 ± 10.9 years (median 12 years). Five- and 10-year resolution rates in this group were $17.9\% \pm 6.2\%$ and $24.5\% \pm 7.2\%$, respectively (Fig. 1). Even in patients who reported symptom resolution, median duration was found to be 2.8 years (range 0.5–10 years).

Total symptom duration positively correlated with the duration of symptoms at time of initial assessment (Spearman's correlation, $\rho = 0.70$; $P < 0.001$) and the presence or absence of atopic disease (median 12 vs. 7 years, Mann–Whitney *U*-test; $P = 0.025$). By contrast, symptom duration was not correlated with patient-related disease severity, gender or age of onset. Whereas the majority of patients (89.7%) tried antihistamines, few reported significant benefit. Examination of patient files

**Figure 1** Kaplan–Meier analysis of the cumulative rate of persistence of cold urticaria in survey responders.

revealed that none of these patients returned for review. Forty-one per cent of patients (16/39) managed their symptoms by restriction of leisure and sporting activities such as swimming, even reported by two patients whose cold urticaria had resolved completely. Of those considered at potential risk of anaphylaxis due to past symptoms or participation in high-risk activities who were advised to wear medical alert jewellery or carry an AAI, only 3/7 patients (43%) and 1/9 (11%), respectively, adhered to this advice.

Discussion

Consistent with previous studies,^{2,3,11–13} we found that cold urticaria commenced most commonly in early adult life, was more common in females, responded poorly to commonly prescribed doses of antihistamines and had low rates of spontaneous resolution. Even in the 9/41 (22%) of patients reporting resolution, median disease duration was found to be 2.8 years. Moreover, the remainder had persistent disease, with 55.3% reporting stable or worsening symptoms. Interestingly, symptom persistence was significantly associated with intercurrent atopic disease, as well as a greater duration of symptoms prior to initial assessment.

While we were only able to obtain follow-up data on 41 (41%) subjects, questionnaire responders did not appear to differ significantly compared to non-responders in terms of baseline demographics. Furthermore, those with more prolonged or severe disease (compared to those whose symptoms have resolved) might be more likely to complete a follow-up survey, consistent with higher rates of cold-induced symptoms and borderline higher rates of anaphylaxis (Table 2). It is also possible that patients might over-report the impact of current symptoms, consistent with relatively higher patient-rated severity scores compared to relatively lower quality-of-life scores suggestive of no or occasional impairment (Table 2). It remains uncertain, however, whether the disparity between severity and quality-of-life scores relates to over-reporting of minor symptoms, or lifestyle modification that results in a minimisation of

impairment on quality of life. In addition, we did not have access to equipment to objectively measure provocation thresholds to determine the temperature at which urticaria appeared.^{14–16} Temperature thresholds are useful as objective predictors of likely disability, given that patients with lower thresholds are generally less impaired than those with a higher temperature threshold, potentially influencing the frequency and severity of symptoms and thus impact on quality of life.^{14–16} There is also the possibility of selection bias, whereby our data (in common with other specialist clinic-based studies^{2,3,11,12,17–20}) have the potential to over-represent disease severity and duration compared to that occurring in the community. Taken as a whole, our data may not necessarily represent the characteristics of the entire population with cold urticaria, but likely reflects the characteristics of a more severe subset of affected patients.

Our 5- and 10-year resolution rates of 17.9% and 24.5%, respectively, are similar to previous reports of 11–18% and 26–35% reported over similar time periods,^{2,3,11} but worse than other forms of chronic urticaria.^{3,12,18–20} The outcome in children with cold urticaria appears to also be bleak, with one study of 30 children aged 2–18.5 years referred to specialty services (tertiary hospital or private allergy practices) reporting resolution in only 7.4% patients over an average of 3 years.¹⁷ In an older cohort of individuals with cold urticaria aged 41.5 ± 15.6 years, those with onset before age 30 years were more likely to have severe or generalised disease,² consistent with the poorer 10-year outcome in our patients whose median age of onset was 17 years.

Perhaps not surprisingly, those with longer duration of pre-assessment duration were more likely to have long-standing disease on follow-up, perhaps related in part to referral bias of those with refractory symptoms. Disparities regarding disease severity and likelihood of persistent disease might in part be explained by definitions of severity (patient assessment; positive relationship between severity and disease duration²) and our study (defined by the presence or absence of anaphylaxis; no relationship between severity and duration). Although it can be argued that our definition of severity suffers the limitations of anaphylaxis being patient reported, subject to environmental exposures (such as cold water immersion) and defined as the presence of one or more events, it is more objective than the potential bias introduced by subjective patient severity scores, as discussed above.

Our data also indicate that atopy (but not other demographic factors such as age of onset) may be a useful prognostic factor for disease duration, albeit with conflicting results from other studies,^{2,3,6,11,17,19} and the potential for higher rates of atopic disease in patients assessed and specifically screened for atopy in a specialist allergy practice. Indeed, an IgE-dependent pathogenesis for cold urticaria has been proposed as one potential explanation for a link between atopy and cold urticaria, with

successful therapeutic trials of anti-IgE reported for managing refractory cases.^{21–23}

As in most cases of chronic urticaria, an underlying cause was rarely found, although reports of preceding infectious illness, adverse reaction to medication or insect stings and higher than expected rates of coeliac disease or autoimmune thyroid disease are consistent with our findings, and the detection of rare B-cell malignancies in occasional patients merits thorough investigation of all patients.^{11,20,24} As in other cases of chronic urticaria, an autoimmune pathogenesis for cold urticaria has been postulated, with IgG autoantibodies directed against IgE or the high-affinity IgE receptor identified in some patients with cold urticaria,²⁵ although their detection is neither sensitive nor specific.²⁴

At least in a subset of patients, cold urticaria is chronic, results in impaired quality of life and significant lifestyle modification and responds poorly to standard or higher doses of H₁ and H₂ antagonists. Although the exact mechanism of mast cell activation and the role of histamine compared to other mast cell mediators (e.g. PAF, leukotrienes, cytokines) in producing symptoms in cold urticaria are ill defined, antihistamines are the treatment of choice for symptomatic relief in patients with chronic urticaria.^{16,26} Recent guidelines suggest that up-dosing of H₁ antihistamines up to fourfold might be effective in patients who do not respond to standard doses of antihistamines.¹⁶ Unfortunately, given the heterogeneity of chronic urticaria, evidence of up-dosing antihistamines is limited to a few dose ranging studies, which suggest that higher than usual doses may alter the temperature threshold at which cold urticaria can be provoked.^{27,28} In this study, our ability to assess the efficacy of antihistamines was undermined by poor adherence to follow-up. Furthermore, advice to move to warmer climates, modify lifestyle or even “desensitise” to cold water^{11,29} seem superficially impractical or unacceptable yet were adopted by many patients in our study in preference to pharmacotherapy. Few patients adhered to recommendations designed to reduce the risk of anaphylaxis, but it remains uncertain whether this reflects low compliance rates in patients with a chronic disorder that mandates routine patient recall, or lifestyle modification by patients who perceive that they have mitigated their risk. Although some individuals may respond to alternative agents, such as immune modulatory agents,^{16,30} there are few studies examining their benefit in cold urticaria as a specific entity, resulting in minimal information to guide treatment in patients where antihistamines are ineffective. The challenges to management of this condition are to encourage review to minimise impact on quality of life and anaphylaxis risk, and to encourage specific trials of non-H₁ antagonists in those with refractory symptoms.

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