Brief Report

Cold urticaria in tropics: A clinico-epidemiological study from North India

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Abstract

Background: Cold urticaria (ColdU) is classified as a subtype of chronic inducible urticaria characterised by recurring pruritic wheals and/or angioedema upon exposure to cold stimuli. However, very limited data is available on ColdU specifically among Indians.

Objectives: The aim of this study was to describe the clinico-epidemiological characteristics and treatment response in North Indian patients diagnosed with ColdU.

Methods: The clinical records of patients diagnosed with ColdU past 5 years (January 2018 to December 2022) were retrospectively reviewed. Data including patient demographics, clinical manifestations, comorbidities, laboratory findings, and treatment response were collected and analysed.

Results: Among the 1780 urticaria patients included in our study, only 15 cases of cold-induced urticaria were identified. ColdU was classified as typical in all but three patients. The mean age of affected individuals was 36 ± 18 years (20–65 years) and eight patients (53.3%) were males. Mean disease duration at presentation was 18 ± 27 months (3 months–4 years). Two patients experienced cold-induced angioedema and one patient had hypotensive episodes following cold exposure. Twelve patients demonstrated positive results in the ice cube provocation test. Of 15, only 6 (40%) achieved complete control of symptoms with standard dosing of second generation anti-histamines while six patients (40%) required titration to higher doses and three patients (20%) were initiated on cyclosporine therapy, resulting in remission.

Limitations: Retrospective study design and possibility of selection bias.

Conclusion: Due to India's predominantly tropical climate, ColdU prevails at lower levels compared to the western regions. ColdU is likely underdiagnosed in India, possibly dismissed as chronic spontaneous urticaria. The management of ColdU involves a combination of protective measures against cold exposure and the use of anti-histamines to control disease activity. This retrospective study provides valuable insights into the clinico-epidemiological characteristics and treatment response of north Indian patients with ColdU.

Key words: urticaria, cold urticaria, cyclosporine, chronic inducible urticaria, cold-induced dermatoses

Introduction

Cold urticaria (ColdU) is a specific subtype of inducible urticaria characterised by the development of wheals with or without angioedema, upon exposure to cold temperatures. The condition is classified as chronic if it persists for more than six weeks.[1] The incidence of ColdU is estimated to be around 0.05% with higher rates observed in countries with colder climates.[2] ColdU can be further categorised as typical

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or atypical. Typical ColdU shows wheals upon rewarming after cold exposure, resolving within an hour. Atypical ColdU refers to uncommon manifestations.[3]

The pathogenesis of ColdU involves various mechanisms, including aberrant temperature sensing, autoimmunity, autoallergy, and neurogenic pathways. Exposure to cold may trigger the formation of autoantigens, leading to an IgE-mediated immune response and subsequent mast cell degranulation.[4] ColdU can also give rise to severe complications, like respiratory distress, disorientation and even shock with some studies reporting rates of up to 20%.[5]

Diagnosis of ColdU is typically based on the clinical history and confirmed through cold stimulation tests, such as the ice cube provocation test or TempTest®. TempTest® conveys temperatures ranging from 4° to 44° C to the patient's skin through a U-shaped aluminum stencil on the device, placed on the inner forearm for 5 minutes. The continuous temperature indication on the U-stencil facilitates the easy identification of the threshold temperature at which wheals are triggered. Management of ColdU involves measures to protect against cold exposure and the use of anti-histamines to alleviate symptoms.

While India is predominantly known for its tropical climate, ColdU is not an uncommon entity, particularly in Northern India, where cold weather persists for 3–4 months with temperatures dropping as low as 1–2°C. Limited data exists on ColdU among the Indian population, necessitating further research to understand the condition better. This study aimed to describe clinico-epidemiological characteristics and treatment responses in our ColdU patients.

Methods

Study population

In this retrospective study, data from patients diagnosed with ColdU referred to the urticaria clinic from January 2018 to December 2022 was analysed. Patient profiles, including demographics, family history, disease severity, physical test results, associated disorders and treatment regimens, were assessed. Disease severity at presentation was evaluated using Urticaria Activity Score 7 (UAS7). Laboratory evaluation included complete blood count (n = 15), serum IgE levels (n = 11), anti-nuclear antibody (ANA) testing (n = 9), thyroid profile with anti-thyroid peroxidase (TPO) levels (n = 9), serum cryoglobulin levels (n = 8) and D-dimer levels (n = 8).

Diagnostic criteria

ColdU was diagnosed based on clinical history from patients experiencing the development of localised wheals, generalised wheals, swelling of acral body parts, angioedema, or systemic symptoms (signs and symptoms of hypotension, difficulty in breathing with wheeze or stridor), following exposure to cold triggers. Records of specific cold triggers were also retrieved, wherever available.

To confirm the ColdU diagnosis, an ice cube provocation test was conducted. Ice cubes, enclosed in a non-latex glove, were applied to the volar aspect of the forearm for five minutes [Figure 1]. A positive result occurred if wheals developed after ten minutes, confirming the ColdU diagnosis.[2] Additional tests for atypical urticaria involved exercising in a cold room for 15 minutes and mechanical stroking post-cold exposure, depending on the clinical scenario.

Statistical analysis

SPSS software conducted the statistical analysis. Descriptive statistics, including frequencies, percentages, means and standard deviations (SD), summarised each variable. Categorical variables were expressed as frequencies and percentages and continuous variables as means ± SD.

Figure 1: The ice cube provocation test, conducted with an ice pack, elicited a positive reaction in a female patient with cold urticaria.

Results

Clinico-demographic characteristics of study population

Among 1780 patients registered in the urticaria clinic during a study duration of 5 years, 570 (32%) patients were diagnosed with chronic inducible urticaria. Among these, 15 patients were identified as having ColdU, accounting for 2.6% of the chronic inducible urticaria cases and 0.8% of all chronic spontaneous urticaria (CSU) cases. All patients had an acquired form of ColdU. The baseline characteristics of the study population are summarised in Table 1.

The most commonly reported trigger was cold air exposure, followed by local contact with cold water, cold water immersion, and contact with cold surface [Table 2]. On the assessment of disease severity, 8 (53.3%) had a history of wheals only localised to the site of exposure, 5 (33.3%) had a history of generalised wheals and 2 (13.3%) presented with systemic features. Four patients demonstrated mild disease activity (UAS7 score range: 7–15), 6 patients had moderate activity (UAS7 score range: 16–27) and 5 patients had severe activity (UAS7 score range: 28–42), respectively. Two patients had concomitant cold-induced anaphylaxis (ColdA) with breathlessness and visible mucosal swelling, associated with a hypotensive episode in one patient. One patient experienced an episode triggered by riding on a motorbike during winter months and another patient developed symptoms upon prolonged contact with cold surfaces [Table 2].

Disease associations and laboratory evaluation

No familial complaints were reported. Atopy was present in five patients (33.3%), hypothyroidism in two patients (13.3%) and two patients (13.3%) had other inducible urticaria forms (symptomatic dermographism and delayed pressure urticaria). CSU occurred in three patients (20%). One patient had allergic bronchopulmonary asthma since age ten with ongoing medication.

The ice cube provocation test showed positive results in 12 patients with localised wheals appearing within 5–20 minutes and lasting 1–4 hours. One patient with cold-induced cholinergic urticaria developed wheals after exercising in a cold room for 15 minutes. Cryoglobulins were not detected in any patient. Serum IgE levels were elevated (>100 IU/ml) in 8/11 patients (72.7%) with a mean value of 771.3 ± 940 IU/ml (76–3027). Four patients (40%) had a high platelet count. Two patients each (22.2%) had a positive ANA test and hypothyroidism with positive anti-TPO antibodies. D-dimer levels were elevated in five patients (62.5%).

Table 1: Baseline characteristics of the study population

Parameter	Value
Mean ± SD age	36 ± 18 years (range: 20–65 years)
Males: Females	8:7
Predominantly outdoor jobs	5 (33.3%)
Mean ± SD total duration of disease	18 ± 27 months (range: 3 months to 4 years)
The mean period between symptom onset and diagnosis	5 ± 8 months (range: 2–18 months)
Typical cold urticaria (ColdU)	12
Atypical cold urticaria	3
- Delayed cold urticaria	1
- Cold-induced dermographism	1
- Cold-induced cholinergic urticaria	1

SD: Standard deviation

Treatment response in cold urticaria patients

Patients received counselling on cold protection measures. All patients were initiated on a standard dose (levocetirizine), and two patients with angioedema also received a short course of oral steroids. During follow-up, 40% of patients achieved complete control with standard dose antihistamines. For those who did not achieve complete control, antihistamine dosage was increased according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines.[6] With higher doses, another 40% of patients achieved complete remission: one patient required to double the standard dose, two patients required a threefold increase and three patients required a fourfold increase. Three patients (20%) with refractor disease were started on cyclosporine therapy at a dose of 3 mg/kg/day in addition to a maximum dose of antihistamines. Two patients with a history of breathlessness were prescribed adrenaline autoinjectors in addition to standard treatment.

Notably, two of the three patients unresponsive to antihistamines had comorbid conditions – hypothyroidism and positive ANA (1:32) in one patient each. All three patients showed improvement within four weeks and complete remission was achieved within ten weeks of initiating cyclosporine treatment. Long-term follow-up data was available for 10 patients with a mean follow up duration of 23 ± 7.228 months (10–47 months). Eight patients maintained stable disease while receiving therapy, while two patients were able to effectively manage their condition through lifestyle modifications alone. Among patients receiving cyclosporine, one patient successfully tapered and discontinued cyclosporine after 9 months, while the other two continued ongoing treatment, surpassing 12 months, emphasising variable treatment response duration in this cohort.

Discussion

The clinical characteristics of patients with ColdU in tropical countries, such as India, remain relatively understudied with limited reports primarily consisting of case reports.[7,8] To address this knowledge gap, we aimed to provide a comprehensive understanding of clinical features and treatment responses among ColdU patients.

A recent meta-analysis reported a pooled prevalence of 7.62% for ColdU among chronic urticaria cases, while a study from Thailand estimated a proportion of 2.5% among chronic urticaria cases.[9,10] Here, we observed a considerably lower proportion of 0.8% among chronic urticaria cases registered during the study period, highlighting the rarity of ColdU in

Table 2: Clinico-epidemiological characteristics of patients

Patient	Age/ sex	Place of residence	Occupation	Duration of disease (months)	Disease severity	UAS7	Trigger(s)	Comorbidities	Associated other forms of urticaria	S. IgE	ANA	Treatment
1	48/F	Himachal Pradesh	Homemaker	48	Localised	21	Local contact with cool liquid	Hypothyroidism	CSU	92	Negative	Cyclosporine with AH
2	35/M	Punjab	Software engineer	4	Localised	18	Local contact with cool liquid	ABPA	-	1054	-	4x AH
3*	21/F	Chandigarh	Student	18	Systemic	35	Contact with a cool surface	-	-	208	Negative	Prednisolone+ 3x AH, adrenaline autoinjector
4*	30/M	Himachal Pradesh	Police officer	48	Systemic	28	Cold air exposure	Atopy	-	1032	Negative	Prednisolone+ 4x AH, adrenaline autoinjector
5	64/M	Uttar Pradesh	Farmer	18	Localised	22	Cold water immersion, local contact with cool liquid	-	-	-	-	Once daily AH
6	46/M	Chandigarh	Salesperson	5	Generalised	16	Cold air exposure	-	-	-	Negative	2x daily AH
7	21/M	Chandigarh	Student	36	Localised	35	Cold air exposure	Atopy	Cholinergic urticaria	917	Negative	Once daily AH
8	35/M	Haryana	Cleaner	36	Generalised	14	Local contact with cool liquid	Atopy	CSU	3027	2+ fine speckled	4x AH
9	48/F	Haryana	Homemaker	24	Generalised	12	Cold water immersion	Hypothyroidism	-	76	-	Once daily AH
10	25/F	Himachal Pradesh	Student	12	Localised	7	Cold water immersion, cold air exposure	-	CSU	-	Negative	Once daily AH
11	55/M	Haryana	Labourer	30	Generalised	32	Cold air exposure	-	-	445	-	Cyclosporine with AH
12	39/F	Himachal Pradesh	Accountant	5	Localised	28	Local contact with cool liquid	Atopy	-	872	-	Once daily AH
13	36/M	Chandigarh	Driver	15	Localised	21	Cold air exposure	Atopy	-	675	Negative	Once daily AH
14	52/F	Punjab	Homemaker	9	Localised	8	Cold water immersion, cold air exposure	-	-	-	-	3x daily AH
15	32/F	Chandigarh	Homemaker	36	Generalised	16	Cold air exposure	-	Symptomatic dermo-graphism	87	3+ fine speckled	Cyclosporine with antihistamines

*Patient 3- had hypotensive episodes and patient-4 had difficulty breathing during attacks. Both patients had a history of angioedema.
ABPA: Allergic bronchopulmonary aspergillosis, AH: Antihistamines, ANA: Antinuclear antibodies, CSU: Chronic spontaneous urticaria, S. IgE: Serum immunoglobulin E, UAS: Urticaria activity score.

the Indian scenario. Association between atopy and ColdU was observed in five patients (33.3%) with elevated serum IgE levels in 8/11 patients (72.7%). Atopy has previously been linked with persistent ColdU.[11] In our study, we recorded hypothyroidism and positive ANA titre in two patients with refractory ColdU.

The recent COLD-CE study detected typical ColdU in 75% of participants, a proportion slightly less than the 80% noted in our patient cohort.[12] COLD-CE study reported the occurrence of ColdA in over one-third of ColdU cases, particularly highlighting associations with oropharyngeal symptoms and pruritic earlobes. In our study, two patients experienced ColdA, both presenting with associated angioedema and oropharyngeal manifestations.

Management of ColdU involves protection measures from cold and the use of standard doses of second-generation antihistamines.[9] In refractory cases, omalizumab or cyclosporine can be considered.[13,14] Among our patients, 40% achieved good control with the standard dose of antihistamines. However, six patients (40%) with severe disease required higher doses of antihistamines and three patients received cyclosporine for symptom control. Due to economic constraints, we utilised cyclosporine as a second-line therapy in our study with favourable responses. There have also been reports on the efficacy of dupilumab in refractory ColdU.[15]

This retrospective study has strengths, including a relatively large sample size of inducible urticaria over a 5-year

period, and comprehensive information on clinical and epidemiological characteristics, treatment response, and associated factors.

Limitations

Limitations include its retrospective nature, single-centre design, lack of exploration into genetic or environmental factors, and unavailability of TempTest.

Conclusion

In conclusion, this retrospective study sheds light on the clinical characteristics, epidemiology, and treatment response of North Indian patients with ColdU. Further research with larger and diverse populations, prospective, and exploration of genetic and environmental factors is needed to deepen our understanding of this condition in tropical regions.

Ethical approval: The data in this retrospective study was anonymised to prevent identification of individual patients.

Declaration of patient consent: Given the retrospective nature of this study and the use of anonymized patient data, individual patient consent was not sought. A waiver of consent was sought from Institute Ethics Committee.

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