Portuguese Journal of Dermatology and Venereology

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Port J Dermatol and Venereol. **ORIGINAL ARTICLE**

Clinical characteristics, diagnosis, and treatment outcomes in chronic cold urticaria: Insights from a 15-year study

Características clínicas, diagnóstico e resultados terapêuticos na urticária crónica ao frio: perspetivas de um estudo de 15 anos

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Abstract

Objectives: The aims are to characterize the clinical profile of CCU, evaluate diagnostic tools (particularly cold stimulation testing), review treatment outcomes and options, and highlight gaps in understanding to inform future research. **Methods:** A retrospective observational study was conducted including all consecutive patients followed at a tertiary allergy center who received a clinical diagnosis of CCU between January 2009 and December 2024. Demographic, clinical, diagnostic, and therapeutic data were extracted from electronic medical records using a standardized data collection form. This constituted a consecutive, non-selected sample of patients evaluated during the study period. Descriptive statistics were used to summarize patient characteristics and clinical findings. Categorical variables were compared using the Chi-square test, and a $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics version 28. The study protocol was approved by the institutional Ethics Committee. Data were analyzed in anonymized form and, given the study design, individual informed consent was waived in accordance with applicable ethical guidelines. **Results:** In our cohort of 82 CCU patients (median age 37 years, 66% female), cold air (63%) and cold water exposure (62%) were the most common triggers and 7% experienced cold-induced anaphylaxis. All patients underwent cold stimulation testing to confirm the diagnosis. Most cases were idiopathic; only 2 patients (2.4%) had secondary causes (cryoglobulinemia or human immunodeficiency virus). Disease severity was mostly mild (77%), but a minority (9%) had systemic reactions, often associated with autoimmune comorbidities. Management was centered on patient education, cold avoidance, and non-sedating H1-antihistamines for symptom control. About 19% achieved complete remission during follow-up. **Conclusion:** While CCU is usually self-limited over the years, it can be life-threatening in severe cases. These findings highlight the need for prompt diagnosis, risk stratification, and individualized management. Ongoing research is needed to elucidate the precise pathogenesis of CCU and to optimize therapeutic strategies, particularly in severe or atypical cases.

Keywords: Chronic urticaria. Chronic cold urticaria. Physical urticaria. Anaphylaxis.

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Received: 03-02-2026
Accepted: 03-05-2026
DOI: 10.24875/PJDV.26000020

Available online: 20-05-2026
Port J Dermatol and Venereol. (ahead of print)
www.portuguesejournalofdermatology.com

Resumo

Objetivos: Os objetivos são caracterizar o perfil clínico da CCU, avaliar ferramentas diagnósticas (particularmente o teste de estimulação pelo frio), rever os resultados e opções de tratamento, e destacar lacunas no conhecimento para orientar futuras investigações. **Métodos:** Foi realizado um estudo observacional retrospetivo que incluiu todos os doentes consecutivos acompanhados num serviço de Imunoalergologia de um hospital terciário com o diagnóstico clínico de UCF entre janeiro de 2009 e dezembro de 2024. Foram extraídos dados demográficos, clínicos, diagnósticos e terapêuticos dos processos clínicos eletrónicos através da utilização de um formulário padronizado de colheita de dados. A amostra foi consecutiva e não selecionada, incluindo todos os doentes avaliados durante o período do estudo. A análise descritiva contemplou as características dos doentes e achados clínicos relevantes. Variáveis categóricas foram comparadas utilizando o teste do qui-quadrado e um valor de $p<0.05$ foi considerado estatisticamente significativo. A análise estatística foi realizada com o software IBM SPSS Statistics, versão 28. O protocolo do estudo foi aprovado pela Comissão de Ética institucional. Os dados foram analisados de forma anonimizada e, considerando o design do estudo, o consentimento informado individual foi dispensado de acordo com as diretrizes éticas aplicáveis. **Resultados:** Na nossa coorte de 82 doentes com UCF (idade mediana de 37 anos, 66% sexo feminino), o ar frio (63%) e a exposição à água fria (62%) foram os desencadeantes mais frequentes, tendo 7% apresentado anafilaxia induzida pelo frio. Todos os doentes foram submetidos a testes de provocação ao frio para confirmação diagnóstica. A maioria dos casos foi idiopática; apenas 2 pacientes (2.4%) apresentaram causas secundárias (crioglobulinemia ou infeção pelo HIV). A gravidade da doença foi predominantemente ligeira (77%), embora uma minoria (9%) tenha apresentado reações sistémicas, frequentemente associadas a comorbilidades autoimunes. A abordagem terapêutica baseou-se na educação do doente, evicção do frio e utilização de anti-histamínicos H1 não sedativos, com controlo sintomático. Cerca de 19% dos doentes atingiram remissão completa durante o período de seguimento. **Conclusão:** Embora a UCF seja geralmente autolimitada ao longo de vários anos, pode assumir um carácter potencialmente fatal em casos graves. Estes achados realçam a necessidade de um diagnóstico precoce, estratificação de risco e abordagem individualizada. São necessários estudos adicionais para clarificar a patogénese da UCF e otimizar estratégias terapêuticas em casos graves ou atípicos.

Palavras-chave: Urticária crónica. Urticária crónica ao frio. Urticária física. Anafilaxia.

Introduction

Chronic cold urticaria (CCU) is a chronic inducible urticaria triggered by exposure to cold stimuli, such as cold air, water, cold surfaces, or ingestion of cold foods and beverages, resulting in the rapid onset of cutaneous wheals and/or angioedema.[1] It predominantly affects young adults, especially females, and has an estimated annual prevalence in the general population of approximately 0.05-0.1%.[2] Typically, CCU lesions develop within minutes of cold exposure (often upon rewarming of the skin) and resolve within about an hour. While usually localized and self-limited, CCU can sometimes lead to systemic reactions; in particular, generalized cold exposure (such as swimming in cold water) may precipitate severe anaphylaxis that is life-threatening.[3] Fatalities, although rare, have been reported under such circumstances. The risk of systemic shock underscores the clinical significance of recognizing and appropriately managing CCU.

CCU is classified as a subset of chronic inducible urticarias, distinguishable by its specific trigger (cold). The condition is heterogeneous. Typical cold urticaria refers to the common form in which patients have reproducible wheals from direct cold contact; these patients usually have a positive cold stimulation test (CST) (e.g., ice cube test) confined to the site of stimulus. In contrast, atypical cold urticarias are a group of less common variants characterized by unusual clinical features or test responses.[1] The atypical subtypes include:

- Systemic atypical cold urticaria: cold exposure triggers systemic symptoms without the typical local wheals
- Localized cold urticaria: wheals occur only in particular cold-exposed areas (sometimes with a fixed, localized pattern)
- Localized cold reflex urticaria: urticarial lesions appear adjacent to, but not directly at, the cold contact site
- Delayed cold urticaria: wheals develop hours after the cold exposure (rather than immediately)
- Cold-induced cholinergic urticaria: generalized pinpoint hives triggered by cold, resembling cholinergic urticaria
- Cold-dependent dermographism: linear wheals induced by mechanical stroking only manifest under cold conditions.

These atypical variants are very rare and often difficult to characterize, highlighting an unmet need for better classification and understanding of atypical CCU.[4] The EAACI/GA²LEN/EDF/UNEV consensus guidelines note that careful history and extended testing are essential for diagnosing atypical forms of physical urticaria.[5] Another way to classify CCU is as primary (idiopathic) vs secondary, where secondary cold urticaria is associated with an underlying condition such as an infectious or autoimmune disease, cryoglobulinemia, or a lymphoproliferative disorder. In practice, true secondary causes are uncommon.[3,6] For instance, cryoglobulinemia (cold-precipitable immunoglobulin complexes) is one known cause of secondary cold urticaria, but the actual incidence of cryoglobulin-associated cold urticaria is very low. In the majority of patients, no underlying disease is identified (primary CCU).

Given the potential severity of CCU and its impact on patients' quality of life, prompt recognition and appropriate management are critical. Diagnosis relies on a thorough history and confirmatory provocation tests, while management includes patient education and pharmacotherapy tailored to disease severity. Many questions remain regarding CCU's epidemiology, optimal diagnostic work-up, underlying mechanisms, and best treatment approaches.[5]

Here, we present a comprehensive review of CCU, combining new clinical data from a 15-year retrospective study with a synthesis of current knowledge from the literature. The aims are to characterize the clinical profile of CCU, evaluate diagnostic tools (particularly cold stimulation testing), review treatment outcomes and options, and highlight gaps in understanding to inform future research.

Methods

Study design and patients

We conducted a 15-year retrospective review of patients diagnosed with CCU at a tertiary allergy center in Porto, Portugal. Patients who presented between 2009 and 2024 with a clinical diagnosis of CCU were included. CCU was defined as a history of recurrent urticarial wheals or angioedema precipitated by cold exposure, lasting ≥ 6 weeks, with or without confirmation by cold provocation tests. We excluded acute (< 6 weeks) cold urticaria and cases where an alternative diagnosis was identified. In total, 82 patients met the inclusion criteria.

Data collection

We extracted clinical and demographic data from medical records using a standardized form. This was a consecutive sample including all patients with CCU evaluated in our department during the study period. Variables collected included sex, age at symptom onset, duration of symptoms, personal and family history of atopy or other diseases, and clinical comorbidities. We recorded the specific cold triggers as reported by patients (e.g., cold air, cold water, cold surfaces, ingestion of cold items). Coexistence of other physical urticarias (e.g., dermatographism and cholinergic) was noted. All patients underwent diagnostic cold stimulation testing (ice cube test and/or TempTest®) to verify cold sensitivity. A positive test was defined by the reproduction of a wheal at the test site. For positive tests, we recorded the critical stimulation time threshold with the ice cube (the minimal exposure time required to provoke a wheal, in minutes) or the critical temperature threshold (CTT) with TempTest® (the warmest temperature that still elicited a reaction, in °C) when available. Patients with negative standard tests but a convincing history of cold-triggered urticaria were classified as having atypical CCU. We assessed each case for possible secondary causes of cold urticaria. Work-up for underlying conditions (such as cryoglobulins, autoimmune markers, and infections) was guided by clinical suspicion and confirmed by extended or specialized tests. Management strategies and clinical outcomes were documented, including patient education on cold avoidance and pharmacologic treatments prescribed. We noted the use of non-sedating H1-antihistamines (at standard or higher doses), leukotriene receptor antagonists (montelukast), systemic corticosteroids, or adrenergic agents (epinephrine auto-injectors for emergency use). Clinical outcomes were assessed from follow-up visits. We categorized outcomes as "resolved" (complete remission of cold urticaria symptoms), "improved" (partial reduction in frequency or severity of symptoms), or "unchanged" after at least 6 months of follow-up from the initial visit. The time frame of follow-up varied (median follow-up duration was not explicitly recorded, but all patients had at least one follow-up visit, and many were followed for several years).

Severity grading

We categorized disease severity for each patient using a three-tier grading system adapted from

Wanderer's classification.[1,7] Type I CCU is defined as localized wheals and/or angioedema limited to cold-exposed skin sites (mild reactions). Type II CCU refers to generalized urticarial eruptions (wheals and/or angioedema beyond the exposure site) without systemic symptoms like hypotension. Type III CCU is defined by the occurrence of systemic reactions (such as hypotension, dizziness, syncope, or other anaphylactic symptoms) in conjunction with cold-induced wheals. This classification was applied retrospectively based on documented symptoms.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and study findings. Categorical variables were compared using Chi-square tests. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 28 (IBM Corp., Armonk, NY).

Literature review

In addition to the retrospective study, we performed a literature review to contextualize our findings and provide a broader overview of CCU. Key articles and reviews from scientific libraries and allergy/immunology journals were selected to supplement the discussion, and their data were extracted for integration into this review.

Results

A total of 82 patients with CCU were analyzed (Table 1). The median age at presentation was 38 years (range 4–77 years, interquartile range [IQR]: 32); 26% (n = 21) had disease onset before 18 years of age, and 66% (n = 54) of patients were female. Symptom onset had occurred at a median age of 31 years (range 1–72, IQR: 29). The duration of symptoms before the initial consultation ranged from 4 months up to 45 years (median duration 5 years). Coexistent atopic and autoimmune conditions were prevalent in this cohort. Allergic rhinitis was reported in 41% (n = 34) of patients and 15% (n = 12) had asthma. Twelve percent of patients had a documented autoimmune disease (6 patients with Hashimoto's thyroiditis, 2 with systemic lupus erythematosus, and 2 with rheumatoid arthritis), and 4% had a history of malignancy (1 patient with Hodgkin lymphoma, 1 patient with breast cancer, 1 patient with urothelial carcinoma). In addition, four patients (5%) had another form of inducible urticaria concurrently: three had symptomatic dermatographism (median disease duration of 2 years, range 0.5-5) and one had cholinergic urticaria (disease duration of 2 years).

Table 1. Patient demographics and comorbidities

Patient characteristics	Value
Total patients	82
Female sex, n (%)	54 (66)
Age at presentation, median (range)	38 years (4–77)
Age at symptom onset, median (range)	31 years (1–72)
Duration of symptoms before first consultation median (range)	5 years (4 months–45 years)
Atopic diseases, n (%) Allergic rhinitis Asthma	46 (56) 34 12
Autoimmune diseases, n (%) Hashimoto's thyroiditis Systemic lupus erythematosus Rheumatoid arthritis	10 (12) 6 2 2
History of malignancy, n (%)	3 (4)
Other inducible urticarias, n (%) Symptomatic dermatographism Cholinergic urticaria	4 (5) 3 1

The clinical triggers for urticarial episodes were documented for each patient. The most frequently identified precipitant was exposure to cold air, reported by 63% of patients (n = 52). Nearly as common was cold water exposure (62%, n = 51); for instance, urticarial flares occurred during swimming, diving into cold water, or even cold showers. Contact with cold objects or surfaces provoked symptoms in 45% of patients. A smaller subset (12%, n = 10) experienced urticaria after consuming cold foods or beverages (like ice-cold drinks or ice cream). Patients described acute pruritus, erythema, and wheals on exposed skin shortly after contact with cold.

All patients underwent cold stimulation testing as part of the diagnostic evaluation. Of the 82 patients included, 56 underwent the ice-cube test and 61 were assessed with TempTest®, with 35 patients having both procedures performed. Forty-four patients (54%) had a positive test response: 30 of 56 patients had a positive ice cube test (with a stimulation time threshold ranging from 1 to 20 min) and 21 of 61 patients had a positive TempTest® result (with CTTs between 9°C and 20°C,

median of 13.5°C, IQR: 10). Nine patients presented positive results to both tests. In some cases, both tests were performed at different time points. The remaining 38 patients (46%) with negative results but with a history strongly suggesting cold urticaria were characterized as having atypical CCU. Work-up for secondary causes was positive in only two patients (2%). One patient was found to have essential mixed cryoglobulinemia and another had human immunodeficiency virus (HIV) infection without criteria for Acquired Immunodeficiency Syndrome. Autoinflammatory conditions were excluded either due to a good response to the proposed treatment or to the absence of correlated symptoms (such as recurrent fever, arthralgia, and fatigue) and analytical findings, including elevated inflammatory markers that would support such a diagnosis. No cases of familial cold autoinflammatory syndromes were identified.[8,9] The results are summarized in table 2.

Using the predefined severity grading, we classified 77% of patients as Type I CCU, 15% as Type II, and 9% as Type III. Table 3 summarizes the features of each severity type and the distribution in our sample.

Seven patients (9%) had a history of cold-induced anaphylaxis, meeting the criteria for Type III. All anaphylactic episodes were reported in the context of heavy cold exposure – specifically, aquatic activities (swimming in cold water or diving) were implicated as the trigger in 100% of these anaphylaxis cases. All of these high-risk patients had been prescribed and trained in the use of epinephrine auto-injectors for emergency treatment. In addition, 15 patients (18%) had experienced episodes of angioedema.

Autoimmune comorbidity was significantly associated with more severe disease: among the 10 patients with an autoimmune disorder, 4 (40%) were Type III, and overall, Type III CCU was over-represented in patients with autoimmune disease ($p < 0.01$). We also found that the typical versus atypical CCU phenotype related to severity: patients with typical cold urticaria had higher rates of systemic reactions than those with atypical presentations (32% vs. 13%), and typical CCU was significantly associated with systemic reaction types ($p = 0.04$).

All 82 patients received counseling on avoidance measures as a foundational management strategy. They were advised to minimize exposure to known triggers. Patients were also educated on recognizing prodromal signs of a severe reaction and on the importance of prompt treatment if anaphylaxis occurs. Pharmacotherapy was tailored to symptom frequency.

Table 2. Triggers and clinical presentation

Patient characteristics	Value
Clinical triggers	
Cold air exposure, n (%)	52 (63)
Cold water exposure, n (%)	51 (62)
Contact with cold objects/surfaces, n (%)	37 (45)
Cold foods or beverages, n (%)	10 (12)
Cold stimulation testing	
Any positive test, n (%)	44 (54)
Ice-cube test performed/positive, n (%)	56/30 (54)
Ice-cube test stimulation threshold	1-20 min
TempTest® performed/positive, n (%)	61/21 (34)
TempTest® critical temperature threshold	9-20°C
Classification	
Typical CCU (positive CST), n (%)	44 (54)
Atypical CCU (negative CST with typical history), n (%)	38 (46)
Secondary causes identified	2 (2)
Essential mixed cryoglobulinemia	1
HIV infection	1

CCU: chronic cold urticaria; CST: cold stimulation test; HIV: human immunodeficiency virus.

Table 3. Severity grading of chronic cold urticaria in the study cohort

Severity type	Clinical description of reaction	Proportion of patients (n)
Type I (Mild)	Localized wheals and/or angioedema at the site of cold exposure; no generalized symptoms.	77% (63/82)
Type II (Moderate)	Generalized wheals and/or angioedema beyond the exposure site, but without hypotension or systemic symptoms.	15% (12/82)
Type III (Severe)	Generalized wheals/angioedema accompanied by systemic symptoms (e.g., hypotension, dizziness, syncope, or other anaphylactic features).	9% (7/82)

Non-sedating H1-antihistamines were the mainstay and used in 76% of patients (n = 62), 36 on a continuous regimen (24 at 1 dose/day, 10 at 2 doses/day, and 2 at 4 doses/day) and 26 on an on-demand basis. A subset of patients received additional medications: systemic corticosteroids were used intermittently in 12% (n = 10), and leukotriene receptor antagonists (montelukast) were prescribed as an add-on in 10% of patients (n = 8). Nine percent of patients (n = 7) were noted to carry emergency epinephrine for self-injection – these

were the patients with a history of anaphylaxis from cold exposure. No patient needed omalizumab.

During the follow-up period (spanning from the first consultation to the time of data collection, ranging from 1 to 16 years), 51% of patients (n = 40) showed improvement in their cold urticaria symptoms, who reported less frequent or less severe reactions than before. Thirty per cent (n = 24) had unchanged disease activity at last follow-up, and 19% of patients (n = 15) experienced a complete resolution of their cold urticaria. No deaths or permanent morbidities occurred in our cohort.

Discussion

Our 15-year study provides a detailed insight into CCU in a real-world allergy practice, and the findings are broadly consistent with the epidemiology reported in the literature. Most patients were female and had adult-onset disease, although a meaningful proportion (10%) developed symptoms in childhood or adolescence, highlighting that CCU should be considered across age groups.[10,11] The 5-year mean duration of symptoms before diagnosis reflects that many patients had longstanding disease by the time they sought specialist care. The vast majority (98%) of CCU in this series was idiopathic/primary, consistent with prior reports that support secondary cold urticaria is rare.[4] Autoimmune comorbidities were more frequently observed in patients with type III CCU, suggesting that immune dysregulation may contribute to more severe phenotypes, although conclusions are limited by sample size.[12] Systemic reactions were more common in patients with typical CCU, possibly reflecting lower cold-reactivity thresholds and greater susceptibility to widespread reactions.[13]

The diagnosis of CCU relies on a typical history with confirmation by the CST, as recommended by current guidelines.[5,6] In our cohort, CST performed using either the ice-cube test or the TempTest® device was positive in approximately 54% of patients (n = 44). Although lower than the 75% positivity reported in the COLD-CE multicenter study, this finding is consistent with the known variability of CST performance and supports its continued role as the cornerstone diagnostic tool in CCU.[14] Not all patients underwent both tests, as some were evaluated with only the ice-cube test or TempTest®, due to device availability, clinical preference, or patient tolerance. Differences in test sensitivity, standardization, operator dependence, disease activity at the time of testing, and the use of only one testing modality in some patients likely contributed to this lower positivity rate. TempTest® offers a standardized temperature gradient, whereas the ice-cube test is less standardized and more operator-dependent, potentially affecting results. Our data on atypical cold urticarial (46% of our cohort, n = 38) reinforce that atypical cases are common. For patients with a compelling clinical history but a negative CST, a more comprehensive diagnostic work-up is recommended. One approach is to perform an extended cold challenge that mimics the patient's trigger.[15] Alternative diagnoses should be considered in cases with negative test results. This approach aligns with the stepwise diagnostic algorithm proposed by Diaz et al.,[3] which recommends additional targeted testing for suspected atypical variants rather than routine extensive screening in the absence of red flags. In our study, such an individualized work-up identified approximately 2% secondary causes: cryoglobulinemia in one patient and HIV infection in another, supporting a selective, history-driven diagnostic work-up.

Management focuses on the avoidance of triggers and pharmacologic therapy to prevent or attenuate reactions.[1] Our practice of counseling on cold avoidance (protective clothing, avoiding swimming in cold water, etc.) is universally recommended, as it can significantly reduce the frequency of episodes.[16] Patients in colder climates or occupations with cold exposure need tailored advice. Despite best efforts, complete avoidance is not always feasible, so drug therapy is crucial for ongoing prophylaxis.

First-line pharmacotherapy for CCU, as with other chronic urticarias, is non-sedating H1-antihistamines.[1] Most patients achieved symptom control with this strategy, often at up-dosed regimens, consistent with guideline-based management of chronic urticaria.[5,15] Antihistamines are safe and generally well-tolerated even at high doses. Our outcome data showed that over half of patients improved, likely in large part due to antihistamine therapy combined with avoidance. Additional therapies were used selectively for patients who do not respond adequately to antihistamines alone or who have frequent breakthrough episodes.[5] Epinephrine autoinjectors were prescribed to patients at risk of systemic reactions (especially those who experienced hypotension, syncope, or respiratory compromise), underscoring the potential severity of CCU in a subset of individuals.[4] They and their close contacts should also be educated on emergency management and to seek immediate medical care if a severe reaction occurs. Fortunately, in our series, all patients with anaphylaxis were successfully managed (with avoidance and ready access to epinephrine). No patients in

our cohort received omalizumab, but its documented success in refractory CCU justifies its off-label consideration in practice, supported by several open-label and retrospective studies.[17] The drug is generally well-tolerated and effective in both adults and children. While optimal dosing is unclear, many experts follow the chronic spontaneous urticaria regimen (150-300 mg monthly). A 2017 placebo-controlled trial (n = 31) demonstrated significant improvement in cold tolerance within 4 weeks[18] and a 2018 meta-analysis confirmed that approximately 90% of patients with chronic inducible urticarias respond at least partially.[19]

The observed remission rate (about one-fifth of patients with spontaneous resolution and half improved) aligns with the notion that acquired cold urticaria is often a self-limited disorder. However, a substantial portion can have longer courses – in our series, some had active disease for over a decade, and the literature likewise notes that CCU can persist 20 years or more in certain individuals,[1] highlighting the chronic burden and psychosocial impact of CCU.

Despite advances in understanding and managing CCU, important gaps remain. The underlying pathophysiology of idiopathic CCU is incompletely understood, diagnostic criteria for atypical variants remain heterogeneous, and reliable predictors of severe reactions are lacking. One multicenter study found that cold urticaria patients with anaphylaxis had higher baseline IgE levels and a higher prevalence of certain genetic markers (like KIT mutations or alpha-tryptasemia) than those without anaphylaxis.[20] These findings need validation but point toward potential future tools for risk assessment. Finally, further clinical trials are needed to guide therapy. Given CCU's relative rarity, international collaboration will be helpful to conduct such studies.

Conclusion

CCU is an important subset of inducible urticarias that exemplify how external environmental factors can trigger profound mast cell-mediated reactions. We integrated a 15-year single-center experience with the broader literature, highlighting several key points. First, CCU typically presents in early adulthood with a female predominance, and while often idiopathic, it can occasionally be associated with underlying conditions or autoimmune disease. Second, the clinical spectrum of CCU ranges from benign localized wheals to severe anaphylactic reactions, with cold air and cold water being the most common inciting factors. Third, the cornerstone of diagnosis is the CST, yet a significant minority of patients has atypical cold urticaria requiring alternative diagnostic approaches. Awareness of atypical variants and thorough evaluation of suspicious cases are essential for accurate diagnosis.

In terms of management, our findings reinforce that most CCU patients can achieve good control through a combination of lifestyle modifications and H1-antihistamine therapy, consistent with current guideline recommendations. It is crucial that patients with a history of systemic reactions are equipped with emergency action plans and epinephrine, as emphasized by both our data and literature. The association we observed between severe CCU and autoimmune markers underlines the importance of screening for comorbid conditions in patients with unusually severe or persistent disease. In addition, no familial cases in our series suggest that hereditary syndromes are exceedingly rare in an allergy clinic setting; nonetheless, clinicians should remain vigilant for red flags (such as early infancy onset, multi-system involvement) that might indicate an autoinflammatory syndrome rather than idiopathic CCU. In conclusion, the insights from our 15-year study contribute to the understanding of CCU's clinical behavior and affirm many of the current paradigms in diagnosis and management.

Future multi-center studies and trials will hopefully advance our ability to predict disease course, prevent severe reactions, and tailor treatments to individual patient needs. For now, a careful, patient-centered approach focusing on education, risk mitigation, and stepwise pharmacotherapy remains the foundation for successfully managing CCU and safeguarding patients against its potential dangers.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the institutional human experimentation committee and in compliance with the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institution's Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. All relevant recommendations were followed.

Statement on the use of artificial intelligence. The authors declare that no form of generative artificial intelligence was used in the preparation of this manuscript.

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