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Review

Cryoglobulins, cryofibrinogens, and cold agglutinins in pediatric cold urticaria: pathophysiological insights and clinical management

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ABSTRACT

Cold urticaria (ColdU) represents a peculiar subset of chronic inducible urticaria (CINDU) that poses significant risks of systemic reactions. While IgE-mediated autoimmunity is known as the primary relevant driver, studies on adults suggest that the presence of cryoproteins, such as cryoglobulins (CGs), cryofibrinogens (CFs), and cold agglutinins (CAs), may radically complicate the clinical picture modifying the disease. This review explores ColdU pathophysiology and diagnostic workup focusing on whether these proteins act merely as bystanders or as key players in driving pediatric disease severity and distinct clinical phenotypes.

KEY WORDS: cold urticaria, cryoglobulins, cold agglutinins, cryfibrinogens

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INTRODUCTION

In children, cold urticaria (ColdU) is frequently regarded as an isolated cutaneous condition, yet its potential for life-threatening systemic reactions (cold anaphylaxis) necessitates a thorough diagnostic work-up. It is characterized by itchy wheals and/or angioedema linked to the response to cooling of the skin and/or mucosa, with or without anaphylaxis. Beyond the standard cold stimulation tests (CST), the role of cryoproteins (CPs) as biomarkers or pathogenic co-factors has remained controversial. Recent studies, including large-scale retrospective analyses, suggest that while CPs are rare, they are far from irrelevant, often signaling more severe disease courses or underlying systemic triggers [1].

EPIDEMIOLOGICAL EVIDENCE AND PREVALENCE

Historically, the prevalence of CPs in ColdU was thought to be high due to selection bias in case reports. Recent systematic reviews and prospective studies provide a more accurate picture. In a comprehensive review of 1,151 adult patients affected by ColdU, the weighted prevalence was 3.0% for cryoglobulins (CGs), 1.1% for cold agglutinins (CAs), and 0.7% for cryofibrinogens (CFs) [1]. A prospective study identified CAs in 46% of a ColdU cohort, although titers were generally low (1-16%) [2]. This suggests that low-titer cryoproteins may be more common than previously recognized, but require specialized laboratory handling to be detected. There are no data in the literature on the prevalence of cryoproteins in ColdU in children.

PATHOPHYSIOLOGICAL MECHANISMS

ColdU is a mast cell-centred disease, in fact various signals cause the release of histamine from mast cells [3] causing the onset of swelling or pruritus. Although the mast cell-activating signals have not yet been well defined and are likely to be heterogeneous, there are various factors to be considered [4]. The classic "two-step" model of ColdU involves the formation of a cold-induced skin neo-antigen and subsequent IgE-mediated mast cell degranulation [5]. Cryogenic exposure may trigger the synthesis of autoantigens, eliciting an IgE-mediated immune response and in sensitized subjects, and this cascade culminates in the cross-linking of surface-bound IgE, leading to mast cell degranulation and subsequent wheal formation, a sign of cold-induced IgE-dependent autoimmunity [4]. However, CPs may intervene through several non-IgE pathways, which include complement activation, blood changes due to erithrocyte agglutination and higher blood levels of tryptase.

CGs belong to a class of immunoglobulins characterized by reversible, temperature-dependent solubility; they undergo precipitation upon exposure to hypothermic conditions and fully re-solubilize upon warming to physiological temperatures [6-8]. *In vivo* studies show that the intravascular precipitation of CGs triggers small and medium-vessel vasculitis across multiple organs, notably the skin, joints, kidneys, and peripheral nerves. The resulting clinical presentation is characterized by paroxysmal purpura, livedo, and acrocyanosis, often complicated by Raynaud's phenomenon, arthralgia, and sensory deficits secondary to peripheral neuropathy [9]. Historically CGs are classified into isolated monoclonal (Type I) or mixed (Types II and III). Type II CGs are mixed CGs with a monoclonal component possessing activity towards polyclonal IgG (mainly IgM-IgG). Type III CGs are mixed polyclonal CGs made of one or more classes of polyclonal immunoglobulins or other molecules. [10]. CGs, particularly mixed types (II and III), can activate the classical complement pathway, generating anaphylatoxins (C3a, C5a) that directly trigger mast cell receptors (MRGPRX2 or C5aR) (Fig. 1) [2].

CFs are abnormal proteins and should be distinguished from CGs since, unlike CGs, they precipitate only in plasma and not in serum [11]. CFs can occur independently or in association with CGs. Malignancies, infections and autoimmune diseases are known to induce the occurrence of CFs. CFs can lead to skin impairment such as Raynaud's phenomenon, purpura and cases of arterial or venous thromboses [12]. Thus, cryoglobulinemia and cryofibrinogenemia (the presence in blood of the respective CPs) are distinct from cryoglobulinemic or cryofibrinogenic diseases or syndromes [8,12]. It's important to underline that healthy subjects may have CGs [13] orCFs [12].

CAs, also known as cold autoantibodies, are primarily IgMs. CAs bind to the I/i antigen on erythrocytes at low temperatures (below 37°C) inducing complement-mediated cell lysis or the release of proinflammatory mediators, modifying the local vessel environment and lowering the threshold for mast cell activation [9].

Recent evidence shows that CG levels correlate with basal serum tryptase, suggesting that patients with higher CP loads may have a higher baseline "priming" of mast cells contributing to mast cell degranulations [2].

DIAGNOSTIC TESTS

In patients presenting with typical ColdU, localized wheal formation is consistently inducible through cold stimulation tests (CST), by applying a cold stimulus to forearm skin utilizing either standardized ice cube challenges or the TempTest system. Patients should cease the use of second-generation H1-antihistamines (sgAH) at least 3 days before testing, while systemic glucocorticoids must be discontinued at least 7 days prior. The sensitivity of an ice cube test is 53-83% and the specificity 97-100% [14,15], but the test does not allow to measure the temperature threshold (CTT). When performing the ice cube test, the cube should be contained within a thin plastic film to prevent thermal skin injury and to exclude potential cross-reactivity with aquagenic urticaria [16]. Cold water immersion is discouraged due to the heightened risk of triggering systemic reactions.

TempTest is a Peltier-effect provocation system designed to deliver a continuous temperature gradient (ranging from 4 to 44°C). This advanced diagnostic tool enables standardized, reproducible cold provocation testing, facilitating the determination of specific temperature and stimulation time thresholds [17]. CST should be performed for 5 min but provocation times may be adjusted based on clinical necessity. A shortened duration of 30 seconds is advisable for highly sensitive patients or those concerned about systemic reactions. Conversely, an extended period of up to 20 minutes may be required for patients with a positive history who do not exhibit wheals during standard testing [18].

For patients presenting with a negative ice cube test, alternative diagnostic methods may be necessary, such as immersing the arm in cold water (5-10°C) for 10 minutes. Assessment of the test site should occur 10 minutes post-provocation. A positive result is defined by the presence of a palpable and clearly visible wheal-and-flare reaction, typically accompanied by pruritus or a burning sensation. In the event of a positive response, threshold testing should be conducted whenever feasible [19]. Cold sensitivity can be characterized by CTTs and critical stimulation time thresholds (CSTTs). Threshold testing aims to identify the minimum stimulation time or temperature required to elicit a response. The CSTT is defined as the shortest duration of cold exposure necessary to induce a positive reaction. This threshold is established by incrementally adjusting the duration of cold application until a wheal-and-flare response occurs. Testing can be performed using either an ice cube or the TempTest device. Notably, stimulation time thresholds of 3 minutes during ice cube testing are indicative of increased disease activity [18]. The CTT – defined as the highest temperature capable of eliciting a positive reaction – can be accurately assessed via TempTest, whereas ice cube testing remains inadequate for this purpose. Whenever accessible, TempTest should be employed to determine these thresholds, as this data empowers patients to mitigate risks in daily life. Furthermore, temperature threshold measurements serve as a vital metric for evaluating disease severity, activity, and therapeutic efficacy [20].

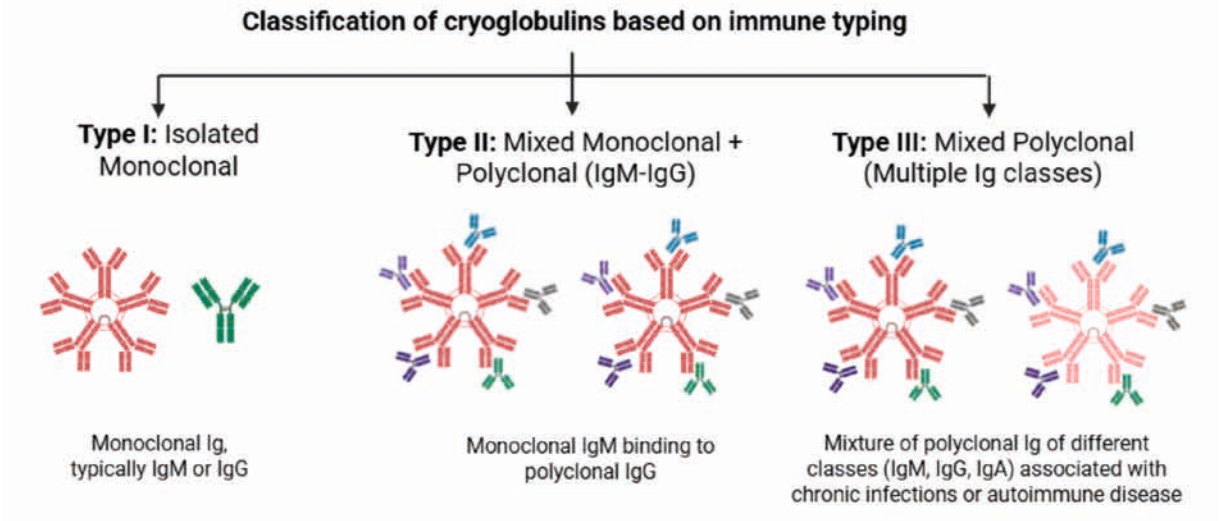

FIGURE 1. Classification of cryoglobulins based on immune typing (adapted from [8]).

CLINICAL PRESENTATION

Although the clinical presentation of ColdU worsens during winter, it is still not completely understand how cold factor triggers a specific clinical presentation of the disease. Typically, patients develop symptoms within 1-5 minutes after cold exposure. The clinical manifestations of ColdU range from localized wheals, to severe systemic reactions, such as respiratory distress, hypotension, gastrointestinal distress, and shock [4]. There is evidence of oropharyngeal angioedema after ingestion of cold drinks or foods [21]. The severity is typically dictated by the intensity and duration of cold exposure, alongside individual sensitivity thresholds. Patients exhibit a broad spectrum of CTTs, varying from below 4°C to above 27°C. Common triggers involve contact with cold surfaces, immersion in cold water, exposure to low ambient temperatures or wind, and the ingestion of chilled foods or drinks [4,22].

While the median duration of ColdU is roughly 6 years, cases persisting for two decades or more have been documented [23]. Clinical predictors for a long-term form of ColdU include early onset, severe disease, and higher CTTs. Overall, the natural history of ColdU, including the progression rate to chronic ColdU, the cause of spontaneous remission and the relapse rate are barely understood. CSTTs have been suggested as a clinical predictor for severe ColdU [23].

The variants of atypical ColdU include Systemic atypical ColdU, localized ColdU, localized cold reflex urticaria, delayed ColdU, cold-induced cholinergic urticaria and cold-dependent dermographism [4]. Systemic atypical ColdU, a more severe form of ColdU, is triggered by general body cooling (such as spending 10-20 minutes in a cold room at 4°C). Localized ColdU might only show symptoms on specific areas like the face, while localized cold reflex urticaria causes tiny, itchy wheals a few centimeters away from the actual point of contact. There is also a delayed ColdU form where the skin remains clear initially, only for the urticaria to appear between 9 and 72 hours later. Cold-induced cholinergic urticaria occurs during exercise in a cold environment, resulting in very small (0.2-0.3 mm) generalized wheals. Another variation is cold-dependent dermographism, where the skin reacts to being scratched or stroked, specifically when it is also exposed to cold temperatures [20].

Cold anaphylaxis (ColdA) may satisfy any of the three diagnostic criteria established by current anaphylaxis practice parameters: (a) acute onset within minutes or hours involving the skin and/or mucosal tissues; (b) the sudden manifestation of two or more symptoms following exposure to a likely trigger (including mucocutaneous, respiratory, cardiovascular, or gastrointestinal signs); or (c) a drop in blood pressure after exposure to a known allergen. However, ColdA appears to be dose-dependent – contingent upon both the extent of the exposed area and the duration of exposure – a characteristic that distinguishes it from classic IgE-mediated anaphylaxis [24].

The presence of CPs appears to delineate specific clinical phenotypes that may be particularly relevant in the pediatric setting. Two different clinical phenotypes have been observed by Bizjak et al [2]. The first is cold agglutinin-positive coldU. Patients testing positive for CAs often exhibit an increased environmental sensitivity (higher rates of reactions triggered by cold ambient air, wind and immersion in water, even when temperatures are not extreme). They also have a poor disease control meaning significantly lower urticaria control test (UCT) scores compared to CA-negative patients. They have extracutaneous symptoms with a higher frequency of angioedema triggered by cold foods or drinks [2]. The second phenotype comprises cryoglobulin-associated ColdU. CG concentrations have been shown to correlate with disease chronicity with a major total duration of ColdU. Elevated CGs, as mentioned before, also correlate with higher basal serum tryptase levels, suggesting a higher burden of mast cell activity [2].

The discovery of CGs or CAs should immediately prompt a search for recent viral triggers, such as infectious mononucleosis, Cytomegalovirus, or Mycoplasma pneumoniae, which remain one of the most common causes of transient cryoproteinemia in children [25].

DIFFERENTIAL DIAGNOSES

In the pediatric population, ColdU is not the only condition manifesting with cold-induced wheals. Differential diagnoses for ColdU include genetic disorders like cryopyrin-associated periodic syndromes (CAPS), as well as phospholipase Cγ2-associated antibody deficiency and immune dysregulation (PLAID) [4,26,27]. Neonatal-onset cold-induced whealing is mostly suggestive of CAPS rather than ColdU. While cold-induced urticarial wheals can manifest across all CAPS subtypes, they are most characteristic of familial cold autoinflammatory syndrome (FCAS). Unlike CAPS, ColdU rarely presents in infancy and typically lacks systemic symptoms such as fever or arthralgia. Furthermore, while ColdU is defined by itchy wheals, patients with CAPS often exhibit a broader spectrum of lesions, including flat, non-pruritic, or minimally itchy wheals and erythematous patches [28]. Cold-induced urticarial rash may also characterize Factor XII-associated cold autoinflammatory syndrome (FACAS). In FACAS, cold-induced wheals typically onset during infancy, appearing within 10-30 minutes of whole-body exposure to ambient temperatures below 15-20°C and persisting for several hours. Notably, FACAS is associated with a negative ice cube or cold water bath provocation test [29]. Rarely, neonatal cold-induced whealing presents as a clinical feature of PLCG2-associated antibody deficiency and immune dysregulation (PLAID). This hereditary disease is characterized by cold-induced urticaria, antibody deficiency, increased susceptibility to infections, and autoimmunity due to genomic deletions in the *PLCG2* gene [27].

DIAGNOSTIC WORK-UP AND MANAGEMENT PERSPECTIVES

In pediatric practice, the search for CPs should be judicious. EAACI guidelines recommend a full blood count and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) as routine [19,30], but CP testing should be reserved for cases with atypical CST results or systemic symptoms (fever, purpura, arthralgia) and suspiscion of secondary ColdU following infectious mononucleosis or other viral (Hepatits C Virus, Hepatitis B Virus) or bacterial prodromes. It is known that bacterial infections, such as with *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*, can cause cold agglutinin disorders. It should be noted that false-negative results are common due to improper sample transport as blood must be collected in pre-warmed tubes and maintained at 37°C until serum separation is complete [1]. Cold avoidance measures are extremely relevant in ColdU. Although low to high dose second-generation H1-antihistamines remain the first and second line therapy in ColdU [19,30,31], CA-positive patients are often refractory in terms of the UCT [2]. Systematic reviews and metaanalyses show nonsedating secondgeneration H1antihistamines (nsAHs) significantly improve ColdU, and updosing up to 4fold further lowers CTTs and CSTTs without additional adverse events [31]. Rupatadine at low to high dose, for example, markedly reduced CTT and CSTT versus placebo with good tolerability [32]. In refractory cases, omalizumab (anti-IgE) has shown remarkable efficacy by stabilizing mast cell activation thresholds and providing clinical relief even in the presence of circulating cryoproteins [33]. A randomized, double-blind, placebo-controlled, multi-center study (NCT04681729) is ongoing to evaluate the efficacy and safety of dupilumab in chronic ColdU [34]. Other currently off-label biologics, such as anakinra (anti-IL-1), etanercept (anti-TNF), reslizumab (anti-IL-5), and dupilumab (anti-IL-4/-13), have shown promise in treating ColdU in adult case reports, highlighting the need for further studies to extend these treatment options to the pediatric population [31].

CONCLUSIONS

Screening for CGs, CFs, and CAs in pediatric ColdU is not mandatory for all patients, but remains a vital tool for those with systemic symptoms, atypical CST, or poor response to therapy. Identifying these proteins allows for a more targeted therapeutic approach, ensuring that underlying triggers or infections are addressed and that the risk of systemic reactions is properly managed.

Conflicts of interest statement

With regards to the present work, the Authors have no conflict of interest to declare.

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