Cold urticaria in children.
How dangerous is it?

George N. Konstantinou, MD, MSc

Head
Department of Allergy and Clinical Immunology
417 NIMTS Military Hospital,
Athens Greece

Scientific Collaborator
Allergy Department and Allergy Research Center
“P & A Kyriakou” Children’s Hospital
Kapodistrian University of Athens
Definition

Cold urticaria is a disorder characterized by the rapid onset of pruritus, erythema, and swelling after exposure to a cold stimulus.
Epidemiology

- Any age group (more common 18-25yo)
  Female predilection 2:1

- Incidence: 0.05%
  Frequency between physical urticarias: 5.2-33.8%
  (higher in regions with cold climate)

- 4th commonest type of chronic urticaria
  (chronic spontaneous, dermographism, cholinergic urticaria)

- Atopy is common
Pathophysiology I

- *in vitro* cold-dependent release of histamine from skin biopsies and
  *in vivo* histamine release in serum after immersing an arm into cold water (Figure)
  
  Kaplan A. NEJM 1981
  Kaplan A. JACI 1975

- Basophils do not release histamine ➔ cutaneous mast cells essential

- cold-transformed antibody plus normal skin antigens reaction
  and/or
  cold-induced skin antigen plus normal antibody reaction?
Pathophysiology II

• Infections (respiratory tract, urogenital tract, oral cavity)
  – Viral (HAV, HBV, HCV, HIV, EBV, HSV, )
  – Bacterial (H.pylori, borrelia *sp*, mycoplasma pneumoniae)
  – Parasites (toxoplasma *sp*)

• Cold-dependent abnormal immunoglobulins
  – cryoglobulins, cryofibrinogens, cold agglutinins
  – Donath-Landsteiner antibody

• Hymenoptera stings

No definite causative relationship has be determined
Triggers

• Cold air (cold/windy weather, air-condition)
• Cold surfaces, objects (handling, touching)
• Cold fluids
• Ingestion of cold foods and liquids
• Aquatic activities
• Restriction of blood flow (e.g. typing)
Clinical manifestations I

- Urticarial lesions usually limited to cold-exposed skin areas
- Patients may experience severe systemic and anaphylactic reactions
- Severity depending on
  - the sensitivity of the patient
  - the potency/degree of the cold stimulus and
  - the duration of the cold stimulus
- Local potentially fatal reactions
  - occlusive oedema
    - of the pharynx due to cold drinks,
    - of the upper airways due to cold air
Clinical manifestations II

- **Skin** ➔ urticaria, angio-oedema
- **Oropharynx** ➔ swelling of the lips, tongue, uvula, pharynx
- **Lower respiratory tract** ➔ wheezing, hoarseness, dyspnoea
- **Gastrointestinal system** ➔ nausea, vomiting, stomachache, abdominal cramps
- **Cardiovascular system** ➔ tachycardia, hypotension
- **Central nervous system** ➔ headaches, disorientation, unconsciousness
Grading severity

- **Type I**: localized urticaria/angio-oedema

- **Type II**: 
  $\geq 1$ episode of generalized urticaria / angio-oedema ± involvement of a second system
  (excluding cardiovascular system)

- **Type III**: 
  severe systemic reactions with 
  $\geq 1$ episode of generalized urticaria/angio-oedema 
  associated with hypotension or coherent symptoms
  (dizziness, fainting, disorientation, syncope)

Wanderer A et al. JACI 1986
Guidelines

• British guidelines
  – Acquired cold contact urticaria
    • *application of melting ice cubes in a plastic bag to the skin for 20 min*
    • *local rapid wealing after re-warming the skin*
    • *if negative, an arm can be immersed in cold water at 5-10°C for 10 min*
  
  – Reflex cold urticaria
    • *Only generalized cooling of the body induces weals and ice-cube test is negative. Wealing can be provoked by cooling the body in a room at 4°C for 30 min.*

• EAACI / GA²LEN / EDF guidelines
  – *cold provocation and threshold test*
Diagnosis I

Ice-cube test
• Cold Stimulation Time Test (CSTT)

Hand immersion test
• cold water
  at 5-10°C
  for 10’

Caution: systemic reactions may occur
Wanderer A. JACI 1990
Diagnosis II

- TempTest®
  standardized cold provocation testing
Diagnostic Classification

- **Acquired Cold Urticaria (ACU)** with a positive CSTT
  - Primary ACU
  - Secondary ACU
    - cryoglobulinemia
    - infectious diseases
    - leukocytoclastic vasculitis
  - Miscellaneous
    - insect stings
    - drugs
    - neoplasms

- **Atypical ACU** atypical responses to CSTT
  - Systemic ACU
  - Cold-dependent dermographism
  - Cold-induced cholinergic urticaria
  - Delayed cold urticaria
  - Localized cold urticaria
  - Localized cold reflex

- **Hereditary Subtypes**
  - Delayed cold urticaria (autosomal dominant)
  - Familial cold auto-inflammatory syndrome (autosomal dominant)

Wanderer A. Immunol Allergy Clin N Am 2004
Diagnostic Evaluation

- Historical or physical evidence of acquired cold induced wheals or angio-oedema
- Positive provocation (cold stimulation) test
- CSTT (and temperature thresholds)
- Negative evidence of underlying diseases
Examinations

- Differential blood count
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)

- Cryoglobulins, cryofibrinogens, cold agglutinins
  - ≈4% of cold urticaria patients may have cryoglobulinemia
  - 3% of patients with cryoglobulinemia may have cold urticaria
Demographics in children

• Age of onset: 7yo (range 0.5-14.5yo)

• Aquatic activity: the most common trigger

• 1 out of 3 had anaphylactic reactions

• 1 out of 4 had experienced hypotension

• 84.2% sensitized to common allergens

Abdullah A et al Pediatrics 2004
Prognosis: Duration

• The course tends to be chronic
• Mean duration ranges from 4.8 to 9.3 years
• The disease resolves  (Van Der Valk PGM et al. BJD 2002)
  – within 5 years in 11%
  – within 10 years in 26%
• Most patients experience symptoms for years regardless of the age of onset
• There is no definite method/test/parameter to predict the duration

Wanderer A et al. JACI 1987
Möller A et al. Hautarzt 1996
Prognosis: Risk factors I

- reported clinical reactions to natural cold exposure

- **sensitivity** of the individual

- trigger’s **temperature** (inverse relation) and

- **time of exposure** (proportional relation)
Prognosis: Risk factors II

- CSTT
- oropharyngeal reactions
- aquatic activities

Probability of anaphylaxis

• 20 children with ACU
  – 10/20 localized or generalized urticaria
  – 10/20 anaphylaxis
  – 15/20 sensitized to at least common allergen

  \[3,2 \pm 1,5\] (+) history of anaphylaxis

• CSTT
  (p-value= 0.030)

  \[7,7 \pm 5,9\] (-) history of anaphylaxis

• CSTT 6 min ➔ threshold

Konstantinou GN, Papadopoulos NG
Treatment I

• Management is based on identification of the
  – triggers
  – specific temperature and
  – exposure time

• Antihistamines (up to x4 the daily recommended dose)

• Emergency medication kit for cases with anaphylaxis
  – Epinephrine
  – Antihistamines

Siebenhaar F et al. JACI 2009
Treatment II

- Leukotriene receptor antagonist

- Ciclosporin
  Marsland AM, Beck MH. Br J Dermatol 2003

- Corticosteroids

- Anti-IgE treatment
  Boyce JA. JACI 2006

- A trial of high-dose penicillin or doxycycline
  Siebenhaar F et al. CED 2007

- Tolerance induction
  Black AK et al. Lancet 1979
Recommendations

- Children should be supervised by someone trained how to use epinephrine autoinjector

- Pretreatment with an antihistamine is recommended

- There are no data suggesting that antihistamines administration in individuals with anaphylaxis prevent systemic reactions

- Higher temperature water (swimming pool vs sea) may still induce reactions

- Avoidance of exposure to cold stimuli is the cornerstone to prevention
Conclusions

- Cold urticaria is uncommon in children and mostly idiopathic
- There is a higher rate of atopy and family history of atopy
- Systemic reactions are common and anaphylaxis occur in 1 out of 3 patients
- CSTT provides important clinical information for the severity and the management of cold urticaria
- Prognosis (evolution, remission) is unknown