

Food-dependent cold urticaria: A new variant of physical urticaria

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Clinical Implications

- This is the first report of food-dependent cold urticaria. Patients with cold urticaria should be additionally asked whether their signs and symptoms are linked to the intake of food.

TO THE EDITOR:

Cold urticaria (ColdU) is a chronic inducible urticaria (CIndU) characterized by wheals, angioedema, or both at skin sites of cold exposure, typically within minutes.¹ ColdU is diagnosed by cold provocation testing, that is, by the exposure of forearm skin to 0°C to 4°C for 5 minutes.^{1,2} Here, we report the first case of food-dependent ColdU (FDColdU). FDColdU is a novel variant of physical urticaria, the most prevalent form of CIndU.

A 37-year-old Thai man developed ColdU, 11 months after moving to the United Kingdom. Notably, whealing occurred only and whenever he was exposed to cold weather (nearly 0°C) shortly after eating beef steak (more than 300 g, independent of whether the steak was rare, medium, or well done). Other foods

TABLE I. Investigations (with negative results) performed in our patient with FDColdU

Laboratory tests			
Complete blood cell counts	Anti-HIV		Total serum IgE
Urinalysis	HBsAg		Antinuclear antibodies
Erythrocyte sedimentary rate	Anti-HBs antibody		VDRL
Serum electrolytes	Anti-HCV		Serum complement level (C3, C4)
Stool examination	Thyroid function tests		Cold agglutinin
Blood urea nitrogen	Anti—thyroid peroxidase		Cryoglobulins
Creatinine	Anti—microsomal antibodies		Cryofibrinogens
Liver function tests			
Autologous serum skin test			
Skin prick tests*			
Fresh 10% wt/vol slurry of beef steak prepared by using ground cooked meat in saline			
Beef	Clam	Coco bean	House-dust mite
Pork	Egg white	Yeast	Mixed Aspergillus
Chicken	Egg yolk	Mosquito	Mixed Penicillium
Cow's milk	Wheat flour	Fire ant	Careless weed
Shellfish mix	Rice	Cat hair	Bermuda grass
Fish mix	Soya bean	Dog epithelium	Cladosporium sphaerospermum
Shrimp	Peanut	Mixed cockroach	
Specific IgE			
Galactose- α -1,3-galactose†	Cow's milk‡	Blue crab‡	Soya bean‡
Alpha-Gal Panel (beef, lamb, pork)§	Shellfish mix‡	Egg white‡	Peanut‡
Gelatin§	Fish mix‡	Egg yolk‡	Hazelnut‡
Cooked beef‡	Crab‡	Wheat flour‡	Chocolate‡
Cooked pork‡	Shrimp/prawn‡	Rice‡	
Chicken‡	Lobster‡	Sesame‡	
Cold provocation tests with and without preceding food intake			
Ice cube test (ice cube in a plastic bag applied to the forearm) for 5 min			
TempTest4.0 applied to the forearm for 5 min			
Patient's arm placed for 5 min in tray filled with ice and water (4°C)			

HBs, Hepatitis B surface; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; VDRL, venereal disease research laboratory.

*Allergens (Alk-Abello; Linciln Diagnostics, Dallas, Texas). Glycerin and histamine (10 mg/mL) were used as negative and positive control, respectively.

†Solid-phase immunoassay: ImmunoCAP.

‡Immunoblot.

§FEIA, Fluorescence enzyme immunoassay.

||TempTest4.0 instrument (Moxie GmbH, Berlin, Germany): The TempTest provides a continuous temperature gradient from 4°C to 44°C. This device can be used for the evaluation of the critical temperature threshold and for assessing disease activity and treatment efficacy in patients with ColdU. Test sites should be inspected and test responses should be assessed 10 min after the end of provocation testing.

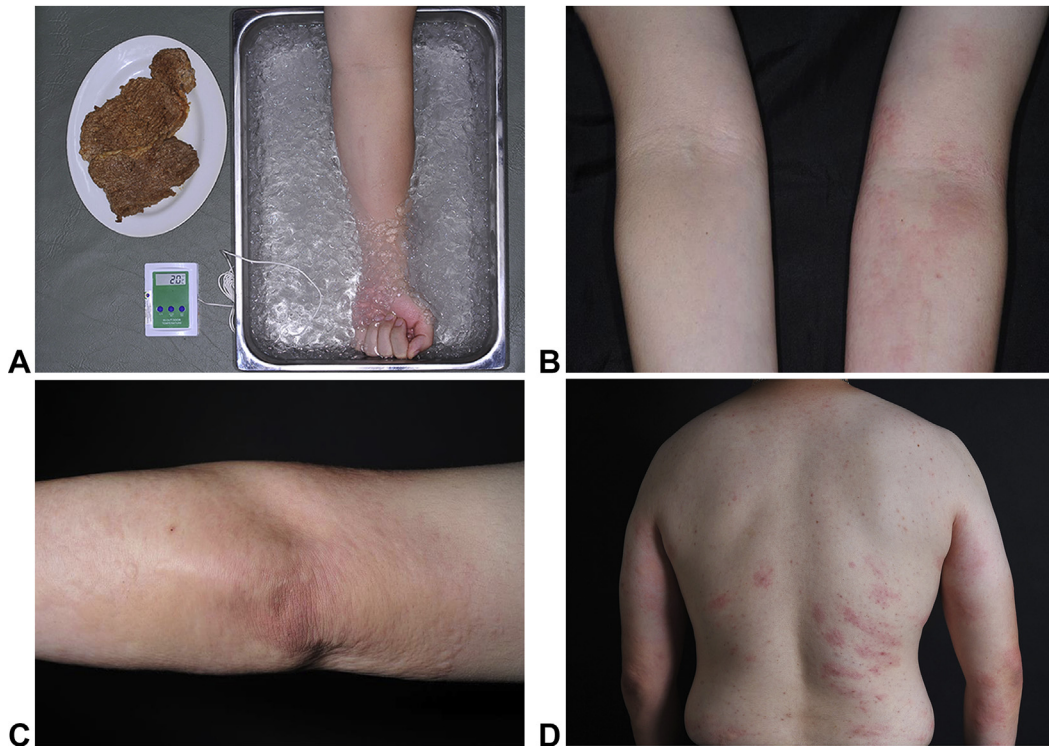


FIGURE 1. Oral food challenge and cold provocation test. **A**, Half an hour after the ingestion of 350 g of cooked beef steak, the patient immersed his left hand and forearm in a tray filled with ice, salt, and water (2°C) for 5 minutes. **B**, Fifteen minutes after the end of provocation, the cold-exposed skin of his left hand and forearm developed multiple itchy wheals, whereas his right arm (control) had no wheals. **C**, The wheals became largely confluent within the following 5 minutes. **D**, Half an hour later, some wheals gradually developed on his trunk and upper torso, without angioedema and systemic symptoms.

including cow's milk and alcoholic beverages were not linked to ColdU. He was otherwise healthy, did not use any medication, and did not recall ever having tick bites.

His physical examination was unremarkable. Results for all investigations as presented in [Table 1](#) were normal. We performed cold provocation tests, first with an ice cube and then with TempTest4.0.^{1,2} The TempTest provides a continuous temperature gradient along its length from 4°C to 44°C. Both test results were negative. We then immersed his left and right hand/forearm in 4°C cold water (ice in water) and 1°C to 2°C cold water (ice and salt in water) for 5 minutes, respectively.³ Results for both these tests were, again, negative.

Next, we performed cold provocation testing preceded by a food challenge. After 12 hours of fasting, our patient ingested 350 g of cooked beef steak. Half an hour later, we first tested with TempTest4.0 for 5 minutes (with a negative result), and we then immersed his left hand/forearm in 2°C water for 5 minutes ([Figure 1](#)). Fifteen minutes after the end of provocation, the cold-exposed skin of his left forearm developed multiple itchy wheals that became largely confluent within the following 5 minutes. Half an hour later, some wheals gradually developed on his trunk and upper torso, without angioedema and systemic symptoms. All urticarial lesions gradually disappeared within 3 hours.

We also performed ice water and salt-based cold provocation tests after the patient had ingested pork, chicken, sea bass, or salmon. All showed positive results. In contrast, ice water and salt-based cold provocation after eating a large portion of rice and

vegetables with only little beef and after eating a large amount of peanuts showed a negative result.

Additional provocation tests demonstrated that the shortest and longest time between a relevant meal and a positive response to cold provocation was 20 minutes and 150 minutes, respectively. Additional skin prick testing with food allergens on pre-cooled skin (2°C water for 5 minutes) produced negative results. We advised our patient to avoid cold exposure after eating any kind of meat or fish and to use desloratadine (5 mg) 1 to 2 tablets when the condition occurs (which he does with a good response).

To our knowledge, this is the first case of FDColdU ever reported. Of note, 2 key features of the FDColdU in our patient have previously been described in patients with “food-dependent exercise-induced anaphylaxis (FDEIA).” First, our patient with FDColdU develops cold-induced wheals only after the ingestion of certain foods, not all foods. This is similar to some cases of FDEIA, where exercise-induced symptoms, in some patients, occur only when preceded by the intake of wheat, eggs, chicken, shrimp, shellfish, nuts, fruits, or vegetables, but not other foods.⁴ Second, cold-induced whealing in our patient is linked to the amount of meat or fish consumed. Small portions do not lead to whealing, large portions reproducibly do. The occurrence and/or severity of symptoms of FDEIA, in some patients, is also dependent on the amount of food eaten.⁵

Our studies clearly demonstrate that both the ingestion of food and skin exposure to cold temperatures are required for wheal development. Notably, FDColdU symptoms in our patient developed only with temperatures below 4°C (critical

temperature threshold of $<4^{\circ}\text{C}$); that is, testing with *TempTest* 4.0 or 4°C cold water with ice gave negative results, whereas provocation with 1°C to 2°C cold water, produced by adding salt in water with ice, showed a positive result.³

The pathophysiology of FDColdU remains to be elucidated. Our patient reported that beef was the culprit food. Our diagnostic workup confirmed that beef, more precisely, at least 300 g of beef eaten between 20 and 150 minutes prior, results in cold-inducible whealing. However, our tests also showed that beef is not the only food that is relevant. Other high-protein meals with other meats or fish also resulted in cold-inducible whealing, whereas low-protein meals with little or no fish or meat did not. One explanation for this is that certain food antigens ingested may become allergens when the skin is exposed to cold temperatures. Interestingly, treatment with anit-IgE (omalizumab) has recently been reported to be effective in ColdU.^{6,7} Clearly, however, our patient is not food allergic, based on the extensive diagnostic workup performed. The fact that our patient shows cold-inducible whealing after some meals, but not all meals, may point to nonimmunologic underlying mechanisms, including effects of high-protein meals on plasma osmolality and pH, blood flow redistribution, tissue enzyme activity, and altered gastrointestinal permeability.⁸

In summary, we report the first case of FDColdU. Patients with ColdU are rarely asked if their signs and symptoms are linked to the intake of food. Doing so may help to identify additional patients with FDColdU, which may improve the management of their disease and may help to gain an understanding of the prevalence and pathogenesis of this novel condition.

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