

Anaphylaxis to Carboxymethylcellulose: Add Food Additives to the List of Elicitors

Ai Ohnishi, MD, Kunio Hashimoto, MD, PhD, Eriko Ozono, MD, Michiyo Sasaki, MD, Ayako Sakamoto, MD, Kasumi Tashiro, MD, Hiroyuki Moriuchi, MD, PhD

A 14-year-old girl developed 4 episodes of anaphylaxis of unknown etiology, which required intramuscular adrenaline administration each time. She had eaten pizza and a cheeseburger immediately before the first 2 episodes, respectively, but had not eaten anything for several hours before the last 2 episodes. It turned out that she had eaten the same ice lolly 4 hours before the first 3 episodes and a Café au lait Swirly (a half-frozen beverage) 4 hours before the last episode. We detected carboxymethylcellulose sodium as the only common ingredient in all anaphylactic episodes. Skin prick tests were positive for carboxymethylcellulose solution and carboxymethylcellulose-containing food products. We obtained a custom-made carboxymethylcellulose sodium-free ice lolly from the manufacturer and confirmed that it did not induce anaphylactic reactions by a challenge test. Carboxymethylcellulose, an anionic water-soluble polymer derived from native cellulose, is considered to be unabsorbable from the human gut and has been widely and increasingly used in pharmaceutical preparations, cosmetics, and food. This article is the first report of anaphylaxis caused by carboxymethylcellulose-containing foods, whereas anaphylaxis to carboxymethylcellulose has been rarely associated with carboxymethylcellulose-containing pharmaceuticals. Although the exact mechanisms underlying the induction of late-onset anaphylaxis by carboxymethylcellulose remain unclear, a small minority of cellulose-digesting microbial flora in the human colon and contamination of food products with carboxymethylcellulose of low molecular weight might be involved. The induction of recurrent anaphylaxis by various products should be a clue that prompts physicians to suspect food additives as a cause for anaphylaxis.

CASE

A 14-year-old girl presented with 4 episodes of anaphylaxis of unknown etiology in the previous 4 months, which required intramuscular adrenaline administration each time. Before then, she had not experienced any allergic responses to food or vaccines and had no history of anaphylaxis or asthma; however, she

experienced an episode of hives of unknown cause and suffered from rhinitis. Immediately before the first episode of hives and dyspnea, she took a bath after eating pizza. The provisional diagnosis was wheat-dependent exercise-induced anaphylaxis; however an immunoglobulin E test specific to wheat, gluten, and omega-5 gliadin, and also a wheat exercise challenge test

abstract

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Dr Ohnishi participated in the patient's medical examination and drafted the initial manuscript; Dr Hashimoto participated in patient's medical examination and assisted in drafting and revising the initial manuscript; Drs Ozono, Sasaki, Sakamoto, and Tashiro provided advice during the medical examination and revised the manuscript; Dr Moriuchi critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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administered after taking aspirin, had negative results. A month later, she developed hives, dyspnea, and facial puffiness while walking to a preparatory school after eating a cheeseburger. While we were preparing for another food-exercise challenge test with cheese, she developed a third episode of dyspnea during the brass band club practice in the evening. She had eaten neither wheat nor cheese. As a matter of fact, she had only eaten an ice lolly in the past 7 hours. In a more careful history taking, we were alerted to the fact that she had eaten the same ice lolly product ~4 hours before all 3 episodes. However, despite avoiding eating an ice lolly, she developed a strange throat sensation and dyspnea again. It turned out that she had consumed a Café au lait Swirle (a half-frozen beverage) and handmade tacos containing cheese, ground meat, and a commercially available sauce and wrapped in tortillas ~4 and 2 hours before the episode, respectively.

At 3.5 hours after a challenge test with the ice lolly, the patient developed dyspnea and hives. However, we were puzzled about the common ingredient in the ice lolly and Café au lait Swirle that could have caused anaphylaxis. Milk was the only item that both food products contained among the 27 possible allergens. However, the patient had never experienced trouble after consuming milk, even after exercise stress. The patient tested negative for immunoglobulin E specific to egg, milk, cheese, tomato, and gelatin (<0.10 kU/L).

We ultimately detected carboxymethylcellulose sodium (CMC-Na) as the only common ingredient that the patient had eaten before all anaphylactic episodes; the ice lolly and Café au lait Swirle contained 145 mg (2.1 mg/mL) and 37 mg (0.23 mg/mL) of carboxymethylcellulose per item, respectively. Prick tests were positive for carboxymethylcellulose solution

(50 mg/mL) and carboxymethylcellulose-containing food products but not for other cellulose derivatives (Fig 1). Because no positive-control histamine solution was available, a wheal diameter of 5 mm or larger was judged to be a positive result, according to criteria for results without positive-control solution in the Japanese Society of Allergology 2013 guideline. At 1 time, 3 healthy individuals underwent the same prick tests, which yielded negative results. Finally, we obtained a custom-made ice lolly from the manufacturer of the ice lolly product, who had omitted CMC-Na from the manufacturing process. It was confirmed by this challenge test that the CMC-Na-free ice lolly did not induce anaphylactic reactions. The patient subsequently avoided any foods containing CMC-Na and had a 6-month period free of anaphylactic reactions until the fifth anaphylactic episode induced by a noodle product containing CMC-Na that she had eaten by mistake.

DISCUSSION

Carboxymethylcellulose, an anionic water-soluble polymer derived from

native cellulose, has been widely and increasingly used in pharmaceutical preparations, wound dressings, cosmetics, and foods (food additive code E466) such as chocolate products, ice creams, frozen cakes, instant pasta, condiments, etc. Anaphylaxis to carboxymethylcellulose is rare and has been associated with carboxymethylcellulose-containing pharmaceuticals, mostly intraarticular injection or infiltration of sustained-release corticosteroids containing a small amount (≤ 10 mg) of carboxymethylcellulose,^{1,2} and rarely contrast medium (barium sulfate preparation) containing a large amount (up to 3000 mg) of carboxymethylcellulose.^{3,4} To our knowledge, this is the first case of carboxymethylcellulose-induced anaphylaxis caused by food products.

Because mammals lack the cellulose-digesting enzyme cellulase, cellulose, including carboxymethylcellulose, was considered to be unabsorbable from the gut, except in ruminants, which depend on the intestinal microbial flora to digest cellulose.

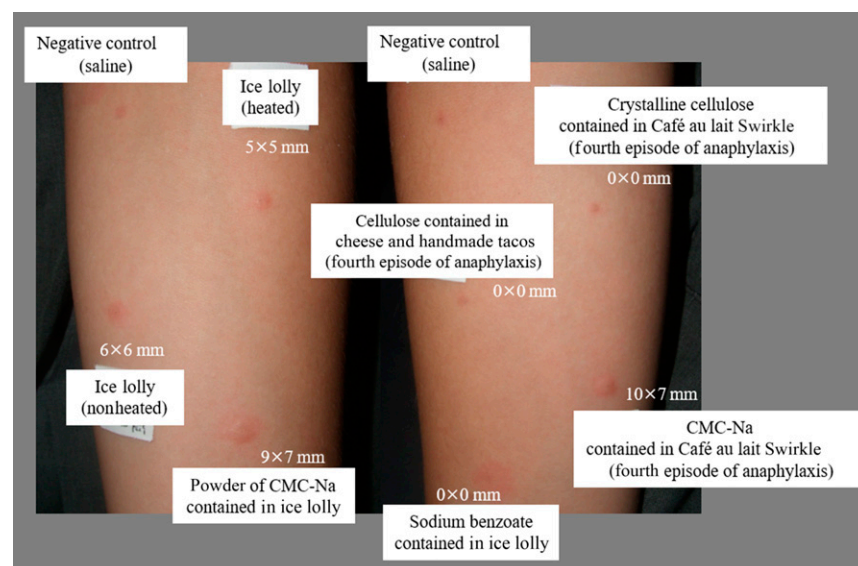


FIGURE 1

Skin prick tests in the patient. A photograph of the forearm taken 15 minutes after inoculation reveals positive reactions to foods containing carboxymethylcellulose but not other cellulose derivatives. The appearance of a wheal with a diameter of ≥ 5 mm was determined to be a positive result.

However, cellulose-digesting microbial flora has also been detected in the human left colon.⁵ The molar mass of carboxymethylcellulose is variable among preparations, depending on the chain length of the cellulose backbone structure. Because the degree of polymerization is influenced by many factors during the production sequence of carboxymethylcellulose, carboxymethylcellulose of low molecular weight, which is presumably reactive and more easily degraded in the gut, might be contained in pharmaceuticals and foods. Therefore, a small portion of dietary cellulose can be slowly broken down and absorbed in the late phase of the human digestion process. Interestingly, all of the 3 previously reported patients with anaphylaxis to carboxymethylcellulose caused by the local injection of corticosteroid preparations had oral provocation tests negative for carboxymethylcellulose (136–250 mg),² suggesting that the absorption of carboxymethylcellulose in the human gut requires specific conditions, such as a specific amount of cellulose-digesting microbial flora.

Although most anaphylactic reactions caused by the aforementioned pharmaceuticals occurred within 30 minutes after administration, our patient required 4 hours to develop anaphylaxis. Liquids can reach the distal colon within 2 hours after oral intake⁶; however it might have taken several hours for a relatively small amount of CMC-Na to be further degraded to low molecular weight by the cellulose-digesting microbial flora in this patient. In addition to its rarity

and the presence of red herrings (wheat and cheese), such late-onset reactions resulted in a delay in the identification of the allergen. However, the exact mechanism underlying late-onset reactions needs to be clarified. In the case of carboxymethylcellulose-induced anaphylaxis caused by barium sulfate preparation, a high carboxymethylcellulose content in barium solutions might lead to a shorter incubation time (~30 minutes).

Why has anaphylaxis caused by carboxymethylcellulose-containing foods never been reported before? It may be due to its rarity or difficulty of making the diagnosis because of its late-onset nature. Although this is the first report of anaphylaxis caused by carboxymethylcellulose-containing foods, it may be underdiagnosed and increasing in frequency because carboxymethylcellulose is being increasingly used in our daily lives. Because it can occur after a long incubation time and because we do not usually know which food products contain carboxymethylcellulose, physicians should carefully take dietary histories and thoroughly investigate the suspected foods for the presence of carboxymethylcellulose. Recurrent anaphylaxis induced by different ingredients should be a clue that prompts physicians to suspect food additives as a cause of anaphylaxis.

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ABBREVIATION

CMC-Na: carboxymethylcellulose sodium

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