

Multiple Chemical Sensitivities Following Intolerance to Azo Dye in Sweets in a 5-year-old Girl

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ABSTRACT

Background: Cases of multiple chemical sensitivities (MCS) have been reported predominantly in adult patients, but pediatric cases have rarely been reported.

Methods: We present a 5-year-old girl who suffered from recurrent reactions accompanied by urticaria, angioedema, headaches, dyspnea, loss of consciousness, and abdominal pain that were not eradicated, but were instead exacerbated, by various treatments with antihistamines and intravenous corticosteroids. Her diet diary revealed that symptoms occurred after ingestion of colorful sweets such as candies and jellybeans. Open challenge tests with food additives and nonsteroidal anti-inflammatory drugs (NSAIDs) were performed after elimination of these items. Skin prick tests using additives and NSAIDs, which were dissolved in saline, and prick-prick tests using candies and jellybeans, were carried out.

Results: Open challenge tests with Tartrazine, aspirin and acetaminophen were positive, whereas skin prick tests using additives and NSAIDs and prick-prick tests using candies and jellybeans were all negative. Consequently, intolerance to azo dyes and NSAIDs such as aspirin was diagnosed. However, she appeared to react to multiple chemical odors such as those of cigarette smoke, disinfectant, detergent, cleaning compounds, perfume, and hairdressing, all while avoiding additives and NSAIDs. On the basis of her history and the neuro-ophthalmological abnormalities, a diagnosis of severe MCS was made and she was prescribed multiple vitamins and glutathione.

Conclusions: The present results suggest that in pediatric MCS, food and drug additives containing azo dyes might play important roles as elicitors.

KEY WORDS

azo dye, food additives, inheritance, multiple chemical sensitivities, nonsteroidal anti-inflammatory drugs

INTRODUCTION

Multiple chemical sensitivities (MCS) syndrome, also known as idiopathic environmental intolerance, is a controversial diagnosis that encompasses a wide range of waxing and waning, symptoms related to more than one body system and provoked by exposure to low levels of chemicals, foods, or other agents in the environment. Although MCS has been studied extensively, a unifying mechanism explaining the illness remains obscure. Cases of adult MCS have been predominantly reported, but pediatric cases are apparently rare. In this report, we present a pediatric case of MCS that appeared to have been triggered by

repeated exposure to food additives such as azo dyes. Notably, the patient's mother had also experienced symptoms of MCS.

CLINICAL SUMMARY

A 5-year-old girl was referred for evaluation after 10 days of recurrent episodes, which were accompanied by generalized urticaria, angioedema, dyspnea, nausea, headache, a slight fever, abdominal cramps, and loss of consciousness, and were not eradicated, but were instead exacerbated, by various treatments with antihistamines and intravenous corticosteroids. She was admitted to our hospital for urgent care and hydration. Her symptoms gradually improved, although

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hives and slight fever did not completely resolve. After discharge, her mother was instructed to keep a diet diary for her. Consequently, the diet diary revealed that hives and angioedema developed immediately after ingestion of sweets containing vivid coloring agents, such as jellybeans and candies, indicating an association between azo dyes and the several events. The association between past recurrent episodes and colorful sweets led her mother to recall that she had eaten a purple-colored candy (found to contain Tartrazine and Brilliant blue 1) immediately prior to the first, severe event. Thereafter, once she began to avoid azo dyes, hives and slight fever rarely recurred.

The patient's mother had suffered from angina, bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, and intolerance to aspirin, theophylline, and lidocaine. She often developed headaches and nausea after being exposed to chemical odors, resulting in a diagnosis of MCS. The patient's father had suffered from frequent urticaria in his childhood.

The past medical history of the patient was bronchial asthma from the age of 2 years. The patient had an incomplete, restricted diet up to the age of 4 years, because her mother was worried that she might be as sensitive as her mother to several drugs, although she had no prior history of reactions to foods or medications. When she was 5 years old, her mother lifted the restriction on medications and foods, hoping to expose her to some drugs and foods so that she would be better able to tolerate the less restricted environment she would experience in kindergarten. The exam for nose, ears, and throat showed no nasal polyp. Blood tests, including a peripheral eosinophil count and serum IgE level, were normal.

To test for hypersensitivity to azo dye and drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), skin testing and open oral challenge tests with Tartrazine (FD&C Yellow No.5, Wako Pure Chemical, Osaka, Japan), Brilliant blue No.1 FCF (FD&C Blue No.1, Kyoritsu Foods, Tokyo, Japan), *p*-Hydroxybenzoic acid (Wako Pure Chemical, Osaka, Japan), aspirin, and acetaminophen were performed under closely supervised conditions, after obtaining the informed consent of her parents. Her parents preferred open challenge tests to blind challenge tests for evaluation. The substances tested were given in the lowest dose. If no objective reaction could be noted, additional and increased doses were given at approximately 3-hour intervals. As a result, the patient tested positive not only to additives such as Tartrazine 300 µg and Brilliant blue No.1 FCF 210 µg, but also to 50 mg aspirin and 10 mg acetaminophen (Table 1). Furthermore, additional challenge tests proved that she is sensitive to other drugs, such as theophylline and lidocaine. According to the standard methods proposed by Dreborg, skin prick tests using

Table 1 Results of challenge tests using additives, NSAIDs, and other drugs

Substance	Symptoms	Dose
Tartrazine (FD & C Yellow No.5)	U, Dy, Ab	300 µg
Brilliant blue No.1 FCF (FD & C Blue No.1)	Dy, He, Ab	210 µg
P-Hydroxybenzoate	—	10 mg
Aspirin	U, He, Ab	50 mg
Acetaminophen	U, Dy, He, Ab	10 mg
Lidocaine (s.c.)	Dy, Ab, Nau	1.25 µg
Theophylline (i.v.)	Dy, He, Nau	6 mg

U, urticaria; Dy, dyspnea; He, headache; Ab, abdominal pain; Nau, nausea.

these drugs and chemicals dissolved in saline were all negative, whereas prick-prick tests using candies, jellybeans, and glutinous starch syrup, which were melted for 1 minute by an electronic oven, were all negative.

Thereafter, she frequently complained of urticaria, dizziness, headache, fatigue, chest tightness, and nausea, although the suspected foods and drugs were avoided. She appeared to react to multiple chemical odors such as those of cigarette smoke, disinfectant, ethanol, detergent, volatile organic chemicals, cleaning compounds, perfume, and hairdressing. On the basis of her history and her neuro-ophthalmological abnormalities, she was given a diagnosis of severe MCS, and prescribed multiple vitamins and glutathione. Her activities had begun to be severely limited due to her symptoms of MCS in public areas. Because she had olfactory symptoms in some areas of our hospital, we set up an air conditioner in a consulting room before her visits. In addition, her mother feared that her imminent transition into public school would likely be made difficult by the school's routine use of stationery, felt-tipped pens and crayons, and cleaning products. School officials permitted an air conditioner to be stationed on beside her in the classroom. Nevertheless, her symptoms appeared to be worsened by the school's use of cleaning products and chalk. Finally, her parents moved from the town to the country, where she could attend elementary school in a wooden frame schoolhouse and experienced no symptoms.

PATHOLOGICAL FINDINGS

Pathological findings were not obtained because her parents did not consent for her to undergo skin biopsy.

DISCUSSION

Despite the numerous agents that are added to foods, there are relatively few documented hypersensitivity

reactions to food additives, especially in children. We report a pediatric case of severe reactions immediately after ingestion of sweets containing azo dyes. Further, our patient developed hypersensitivity not only to food additives but also to multiple other chemicals, including aspirin. The recurrent reactions due to azo dyes might have been a kindling phenomenon of the subsequent symptoms in response to various chemically-unrelated compounds because the first reactions to azo dyes, which were most severe, were consecutively followed by these symptoms. However, the pathogenic link between these two events has not yet been elucidated in the present case.

The prevalence of food-additive intolerance in children age 5–16 is 1–2%,¹ whereas in children aged less than 10 years, including children with asthma, the prevalence of aspirin intolerance is less than 10%.² Carefully blinded studies have shown the incidence of a cross-reaction between aspirin and Tartrazine as a representative of azo dyes to be less than 2.4% in asthmatic patients.³ Unlike in aspirin, the most likely mechanism for reactions to Tartrazine has been reported to be dose-related histamine release from mast cells.⁴

In our patient, not only food additives but also the drugs administered for treatment, which contained several additives such as Food Yellow No. 5 (Sunset Yellow FCF) and sodium benzoate aggravated her symptoms before she was diagnosed. Children might be more frequently exposed than adults to multiple chemicals such as vibrantly colored foods and medications. The original statement concerning adverse reactions associated with pharmaceutical excipients, which was issued by the American Academy of Pediatrics in 1997, warned that although many excipients have been implicated in causing adverse reactions, and these are the most significant in the pediatric population.⁵ An outline of the diagnostic criteria of MCS in children based on those in adult cases was presented by Woolf.⁶ Because there is no single objective test finding to confirm the diagnosis of MCS, its diagnosis in children will often depend largely on historical information obtained from the parents. Olfactory warning of inciting odors appears to be a hallmark of MCS. A mechanism of neurotoxicity from chemical toxicants carried to the central nervous system by way of the olfactory bulb has been offered as

one mechanism of causation.⁷ A significantly higher prevalence of the panic disorder-associated cholecystokinin B receptor allele 7 has been reported in subjects with idiopathic environmental intolerance, as a synonym of MCS (9/22 [40.9%]), compared with control subjects (2/22 [9.1%]).⁸ It should be noted that her mother had also suffered from MCS, indicating that MCS might be a hereditary disorder in a portion of the MCS population.

In the present case, a mother-child relationship seems to have been one of the key factors in the development of clinical symptoms. In this study, challenge tests were openly conducted because informed consent was not obtained from the parents for double-blind tests. Double-blind tests should, however, have been carried out to rule out various factors, including emotional factors. Additional medical examinations as well as socio-medical and psychological approaches to both the patient and her mother need to be carried out in the future.

The present results suggest that in pediatric MCS, food and drug additives containing azo dyes might play important roles as elicitors. Clinicians should therefore consider this possibility before patients with additive intolerance definitively develop MCS.

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