

# Vaccine-induced anaphylaxis in a child with cow's milk allergy: Lactose hydrate was the culprit



Shoko Yoshino, MD,<sup>a,b</sup> Yukiko Hiraguchi, MD, PhD,<sup>a,c</sup> Mari Tatekawa, MD,<sup>a</sup> Tomoya Shingaki, MD,<sup>a,d</sup> Yusuke Kumagai, MD,<sup>a</sup> Yuko Ebishima, MD,<sup>e</sup> Takahiro Kiyomasu, MD, PhD,<sup>a</sup> Kenji Owa, MD,<sup>a</sup> Yutaka Suehiro, MD,<sup>a</sup> Mizuho Nagao, MD, PhD,<sup>c</sup> and Takao Fujisawa, MD, PhD<sup>c</sup>  
*Osaka, Kobe, Tsu, Naha, and Toyonaka, Japan*

Lactose hydrate was the cause of vaccine-induced anaphylaxis in a child with severe milk allergy. Although the amount of milk protein in lactose-containing vaccines is extremely small, physicians administering such a vaccine must be prepared for the potential risk of severe milk allergy. (*J Allergy Clin Immunol Global* 2022;1:87-9.)

**Key words:** Anaphylaxis, cow's milk allergy, Japanese encephalitis vaccine, lactose hydrate

Japanese encephalitis (JE) virus is the cause of the potentially fatal viral encephalitis that is endemic in the Southeast Asia and Western Pacific regions. Although JE vaccines are generally safe, sporadic cases of anaphylaxis as a vaccine adverse event (ie, 0.42 cases per million vaccinations in 2013-2020) have been reported in Japan.<sup>1</sup> The cause of anaphylaxis, however, has not been well described. Here, we report a case of anaphylaxis following JE vaccination of a child with cow's milk allergy, and by using the basophil activation test (BAT), we confirmed the lactose hydrate in the vaccine as the culprit allergen.

The patient was a 3-year-old boy with milk allergy, egg allergy, and allergic rhinitis. He avoided milk from the age of 7 months, at which time he had manifested symptoms of urticaria after eating a food containing skimmed milk powder. At the age of 3 years, he was able to consume a bread containing a small amount of milk (about 0.1 mL of milk per slice) without any symptoms. However, 1 month later, he started to feel itching of the tongue after eating the same bread. At the age of 3 years and 6 months, he received the

## Abbreviations used

BAT: Basophil activation test

JE: Japanese encephalitis

first dose of a JE vaccine (ENCEVAC [Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan]) at a local clinic. He developed a cough and generalized urticaria 40 minutes after the vaccination. He was transferred to an emergency hospital, and anaphylaxis was diagnosed. Intramuscular epinephrine and an intravenous corticosteroid alleviated the symptoms. Later, he was referred to our department to determine the cause of the anaphylaxis.

His serum total IgE level measured by ImmunoCAP was 530 IU/mL, and his antigen-specific IgE levels were 86.10 UA/mL for milk, 91.60 UA/mL for casein, 22.70 UA/mL for  $\alpha$ -lactalbumin, and 0.94 UA/mL for  $\beta$ -lactoglobulin. Anaphylaxis due to the lactose hydrate in the JE vaccine was suspected, and a skin prick test using the ENCEVAC vaccine was performed. To determine whether it would be possible to resume vaccination of this child, the JE vaccine of another company (JEBIK V [The Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan] was also tested (see Table E1 in the Online Repository at [www.jaci-global.org](http://www.jaci-global.org)). The skin prick test result was positive with the ENCEVAC vaccine (wheal diameter 11  $\times$  16 mm) but negative with the JEBIK V vaccine (wheal diameter 0  $\times$  0 mm) (see Table E2 in the Online Repository at [www.jaci-global.org](http://www.jaci-global.org)). BATs were also performed on the antigens and additives of the ENCEVAC and JEBIK V vaccines, as described elsewhere.<sup>2</sup> The components of the vaccines were provided by each manufacturer. Because we were not allowed to use those components for human experiments such as skin prick tests, we used the BAT to investigate for the IgE reactivity for each component. The ENCEVAC vaccine gave positive BAT results with the patient's blood but not with the blood of subjects with no JE vaccine allergy (Fig 1, A). In contrast, the reactions by JEBIK V vaccine stimulation were clearly low (Fig 1, B). In addition, expression of CD203c was enhanced in a concentration-dependent manner with the lactose hydrate used in the ENCEVAC vaccine, whereas the results for the JE virus antigen and other additives were negative (Fig 2).

Thus, the lactose hydrate added to the ENCEVAC vaccine was considered to be the cause of anaphylaxis in this patient. The milk proteins in the lactose hydrate were measured by using Morinaga FASPEK Elisa II Milk (casein) (Morinaga Scientific Institute, Inc, Yokohama, Japan) and FASTKIT ELISA, version III Milk (NH Foods Ltd, Ibaraki, Japan). The manufacturer did not have any lactose hydrate left from the same lot used in the ENCEVAC

From <sup>a</sup>the Center of Allergy and Clinical Immunology, Department of Pediatrics, Osaka Saiseikai Nakatsu Hospital; <sup>b</sup>the Department of Pediatrics, Kobe City Hospital Organization Kobe City Medical Center West Hospital; <sup>c</sup>the Institute for Clinical Research, Allergy Center, National Hospital Organization Mie National Hospital, Tsu; <sup>d</sup>the Department of Pediatrics, Naha City Hospital; and <sup>e</sup>the Kamesaki Children and Allergy Clinic, Toyonaka.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 20, 2021; revised January 23, 2022; accepted for publication January 25, 2022.

Available online March 9, 2022.

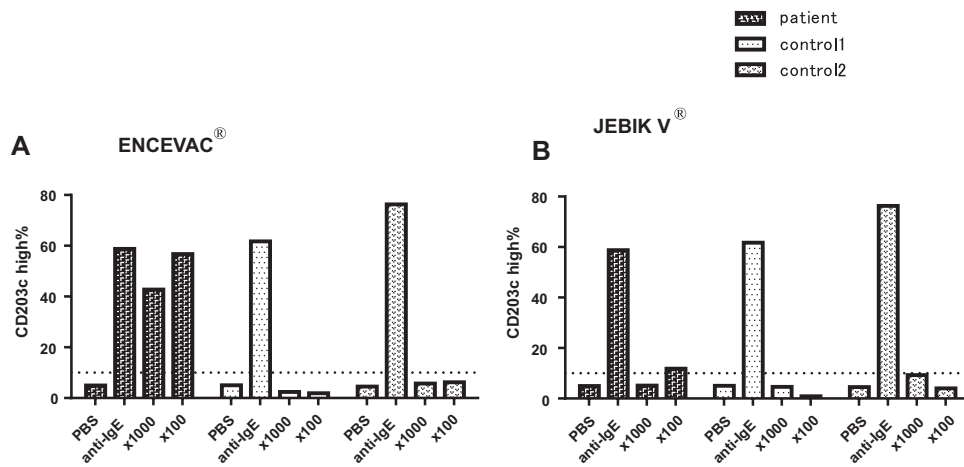
Corresponding author: Yukiko Hiraguchi, MD, PhD, Center of Allergy and Clinical Immunology, Department of Pediatrics, Osaka Saiseikai Nakatsu Hospital, 2-10-39 Shibata, Kita-ku, Osaka 530-0012, Japan. E-mail: [y\\_hiraguchi@nakatsu.saiseikai.or.jp](mailto:y_hiraguchi@nakatsu.saiseikai.or.jp).

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

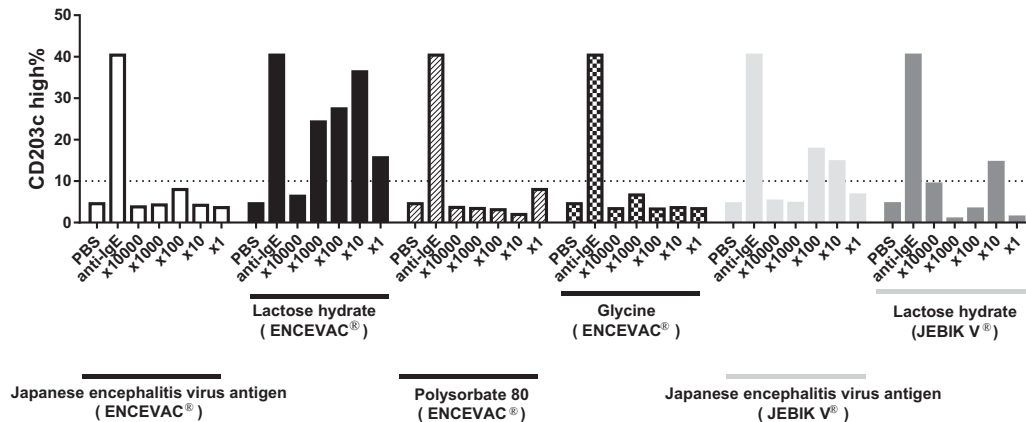
2772-8293

© 2022 The Author(s). Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jacig.2022.01.003>



**FIG 1.** A, Expression of CD203c on basophils incubated in the presence of the JE vaccine administered to this case patient. B, Expression of CD203c on basophils incubated in the presence of another JE vaccine. Anti-IgE antibody served as the positive control, and PBS served as the negative control.



**FIG 2.** Expression of CD203c on basophils incubated in the presence of each component of the JE vaccines. Anti-IgE antibody served as the positive control, and PBS served as the negative control.

vaccine with which the patient was vaccinated. Accordingly, 2 samples from different lots were measured, and 2.6  $\mu\text{g/g}$  of milk protein was detected in 1 lot only with FASTKIT ELISA, version III Milk, which measures multiple milk proteins. A kit that measured only casein did not detect milk protein in either lactose hydrate lot.

Vaccine components known to cause hypersensitivity include active ingredients (antigens) that induce immune responses, as well as residual animal proteins such as milk, egg proteins and gelatin, antimicrobials, preservatives, stabilizers, and adjuvants.<sup>3</sup>

This article is the first to report performance of the BAT on antigens and additives of a vaccine. We clearly show that lactose hydrate is the component that caused the anaphylaxis.

Lactose, a disaccharide found in mammalian milk, is obtained industrially by isolating and purifying it from milk, and it has been used in pharmaceuticals for many years. Lactose hydrate is utilized as an excipient in various medications, including JE vaccines. Because lactose is purified from whey, it may contain residual milk protein.<sup>4</sup> A child with cow's milk allergy exhibited acute allergic

symptoms after inhaling milk sugar-containing dry powder-type bronchial asthma drugs,<sup>5</sup> and acute allergic symptoms were caused by the lactose hydrate added as a stabilizer for injectable steroids.<sup>4</sup> Cases in which infants with cow's milk allergy developed anaphylaxis after diphtheria, pertussis, and tetanus vaccination or oral polio vaccination have also been reported, and the presence of casaminoate,<sup>6</sup> a mix of amino acids and casein-derived small peptides, in diphtheria, pertussis, and tetanus vaccine and  $\alpha$ -lactalbumin in oral polio vaccine has been confirmed.<sup>7</sup> Milk proteins other than casein and  $\beta$ -lactoglobulin may also be contained in the lactose used in Japanese pharmaceuticals.<sup>8</sup>

In this study, we detected milk protein in lactose hydrate when using a kit that measured multiple milk proteins but not when using a kit that measured only casein. This result is consistent with the findings of previous reports.<sup>6,7</sup> Because the threshold for milk to induce symptoms of vaccine-induced anaphylaxis is not clear and because patients such as the patient in this case report are presumed to be extremely rare, we believe that milk allergy in itself is not a contraindication to lactose-containing vaccines.

Nonetheless, as vaccine-induced anaphylaxis is always a possibility, all physicians who administer vaccines should be prepared to deal with anaphylaxis.

In cases of allergic symptoms after vaccination, subsequent vaccination is problematic. In the case reported here, we decided to perform additional vaccination using the JEBIK V vaccine, which gave a negative prick test result and a weak BAT reaction. We vaccinated the patient with divided doses according to the method recommended by the American Academy of Pediatrics,<sup>9</sup> and the vaccination was successfully completed without development of any allergic symptoms. Identifying the causative agent of anaphylaxis, as we did in this study, helps us determine how to more safely vaccinate patients with a history of vaccine-induced anaphylaxis without skipping necessary vaccinations.

#### REFERENCES

1. Documents from the 50th meeting of Working Group Meeting on Adverse Events, the Subcommittee on Vaccination and Vaccines of the Health Sciences Council held in December 2020. Available at: <https://www.mhlw.go.jp/content/10601000/000709484.pdf>. Accessed October 3, 2021.
2. Tokuda R, Nagao M, Hiraguchi Y, Hosoki K, Matsuda T, Kouno K, et al. Antigen-induced expression of CD203c on basophils predicts IgE-mediated wheat allergy. *Allergol Int* 2009;58:193-9.
3. Nagao M, Fujisawa T, Ihara T, Kino Y. Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine-associated anaphylaxis. *J Allergy Clin Immunol* 2016;137:861-7.
4. Santoro A, Andreozzi L, Ricci G, Mastrorilli C, Caffarelli C. Allergic reactions to cow's milk proteins in medications in childhood. *Acta Biomed* 2019;90:91-3.
5. Janie Robles LM. Hypersensitivity reaction after inhalation of lactose-containing dry powder inhaler. *J Pediatr Pharmacol Ther* 2014;19:206-11.
6. Kattan JD, Konstantinou GN, Cox AL, Nowak-Wegrzyn A, Gimenez G, Sampson HA, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. *J Allergy Clin Immunol* 2011;128:215-8.
7. Parisi CA, Smaldini PL, Gervasoni ME, Maspero JF, Docena GH. Hypersensitivity reactions to the Sabin vaccine in children with cow's milk allergy. *Clin Exp Allergy* 2013;43:249-54.
8. Sakai S, Adachi R, Miyazaki T, Aso Y, Okuda H, Teshima R. [Studies on the food allergenic proteins contained in pharmaceutical excipients]. *Kokuritsu Iyakuin Shokuhin Eisei Kenkyusho Hokoku* 2012; 130:58-65.
9. Fritsche PJ, Helbling A, Ballmer-Weber BK. Vaccine hypersensitivity—update and overview. *Swiss Med Wkly* 2010;140:238-46.