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Letter to the Editor

Cord blood eosinophilia precedes neonatal onset of food-protein-induced enterocolitis syndrome (FPIES)

Dear Editor,

Food allergies can be categorized as IgE-mediated and non-IgE-mediated food allergies, depending on whether specific IgE antibodies are the primary mechanism for recognizing offending foods.[1] IgE-mediated food allergies are usually due to sensitization to a food through eczematous skin, and symptoms usually start several months after birth. However, in many patients with non-IgE-mediated gastrointestinal food allergy (non-IgE-GI-FA), symptoms start within one month after delivery.[2,3] Because non-IgE-GI-FAs involve immunity, we hypothesized that acquisition of immunity against offending foods precedes the onset of symptoms after birth, i.e., intrauterine antigen priming or acquisition of immunity. A recent study demonstrating the presence of major food allergens in amniotic fluid supports this hypothesis.[4] However, no studies have investigated the immunological cell types in cord blood of infants with non-IgE-GI-FAs. Because patients with a non-IgE-GI-FA often show significant blood eosinophilia,[5] we reviewed the data on cord blood eosinophils in those patients and compared them with matched controls to test our above hypothesis. Among the non-IgE-GI-FA subgroups, we focused on food-protein-induced enterocolitis syndrome (FPIES), for which there are well-developed diagnostic criteria.

This is a retrospective case−control study. The patient inclusion criteria were: (1) delivery in the National Center for Child Health and Development (NCCHD, Tokyo, Japan) and performance of cord blood examinations, (2) onset of symptoms before one month of age, (3) observation of vomiting more than twice at first presentation, without any other cause for the symptoms, and (4) elicitation of gastrointestinal symptoms (repetitive vomiting and/or frequent diarrhea) within 24 h after oral food challenge (OFC) performed at least 2 weeks after resolution of the initial symptoms. The exclusion criteria were: (1) cord blood clotting and thrombocytopenia of less than $100 \times 10^3/\mu L$, (2) cord blood nucleated red blood cells exceeding 5% and (3) absence of vomiting (to confirm that the symptoms are definitely induced by ingestion of the offending food). Namely, we excluded neonates who were diagnosed with food-protein-induced allergic proctocolitis (FPIAP) or food-protein-induced enteropathy (FPE), without vomiting. As matched controls, 30 babies were randomly extracted from 16,018 babies who did not have FPIES; they were comparable to the 6 patients with FPIES in terms of the gestation period, sex, mode of delivery and birth weight. Supplementary Figure 1 shows the procedures that were followed for selection of the FPIES patients and matched controls. White blood cell (WBC) differentials of cord blood and peripheral blood samples were determined using an automated cell counter (Advia 120; Siemens Health Care Diagnostics; Tokyo, Japan). Blood cells were stained with peroxidase and differentiated by flow cytometry. The study was performed according to a protocol approved by the institutional review board of NCCHD (#2154).

Among 22,459 babies born in NCCHD between March 2002 and March 2015, 7 newborns who had valid cord blood data and experienced vomiting after being started on cow's milk were diagnosed with FPIES based on positive OFC results. One of those patients was excluded due to late onset of symptoms. The remaining 6 patients were enrolled, and their demographics were compiled (Table 1). Serum IgE specific to cow's milk protein was positive in one patient, but vomiting started 3 h after ingestion of milk. None of the 6 patients showed any immediate-type reactions such as acute urticaria or wheezing. The precise clinical data at onset and OFCs are shown in Table 1 and Supplementary Results. Patients 1 and 3 showed repetitive vomiting within 4 h after an OFC, and fulfilled the criteria for chronic FPIES set forth in the consensus guideline.[6] Patients 4 and 5 showed delayed onset (6−7 h) of vomiting after OFCs. Patients 2 and 6 showed frequent diarrhea within 24 h after OFCs. Among the three subgroups of non-IgE-GIFAs, Patients 2, 4, 5 and 6 showed strong similarity to FPIES, but not to FPE or FPIAP. Also, four patients fulfilled the earlier criteria for FPIES.[7] Therefore, all six patients were handled as FPIES in this report.

The laboratory data for the cord blood were compared between the FPIES patients and the matched controls (Fig. 1A). Among the cord blood hemoglobin, WBCs, platelet count and WBC differential, only the cord blood eosinophil percentage was significantly higher in FPIES ($P = .0002$). The absolute count of cord blood eosinophils was also significantly higher ($P = .0001$, Fig. 1B). There was no correlation between the eosinophil count in the maternal peripheral blood and the cord blood of babies with FPIES (Fig. 1C, D). Therefore, fetal eosinophilia is probably not due to simple transfer of eosinophilia-promoting factors from the mother. Eosinophilia may be a result of prolonged eosinophil survival or exaggerated eosinophilopoiesis due to IL-5 overproduction, presumably by

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