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Food Protein-Induced Enterocolitis Syndrome In Two Exclusively Breastfed Infants.

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To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE)- mediated gastrointestinal food hypersensitivity characterized by profuse and repetitive vomiting, severe diarrhea, leading to dehydration and lethargy in infants (1). Although cow's milk and soy protein are
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the most common triggers, FPIES can be triggered by other proteins, such as rice or oat, particularly in infants who have had a previous reaction to cow's milk or soy (1). It has been reported that 0.34 % of infants were diagnosed with FPIES in a birth-cohort (2). FPIES to cow's milk in exclusively breastfed infants is rare. A few cases of FPIES have been reported in exclusively breastfed infants so far (3,4). Here, we report two cases of FPIES described even in exclusively breast-fed infants in which symptoms occurred after maternal ingestion of cow's milk.

The first patient, a 15-day old boy, reporting fever, intermittent vomiting, and diarrhea was admitted to neonatal intensive care unit with a pre-diagnosis of sepsis and dehydration. The patient was exclusively breastfed and did not gain weight due to diarrhea 10-15 times and sometimes more per day. After hospitalization an intravenous fluid resuscitation therapy was implemented. Blood tests showed elevated white blood cell count with mild neutrophilia (white blood cells, 16840/ μ l; neutrophils, 13790/ μ l). C-reactive protein and procalcitonin were negative. Patient's investigations (blood, urine and stool cultures) for infection were negative. The patient was tried breastfeeding the next day, however he suffered repetitive vomiting and pallor. Intravenous rehydration treatment was then given. Repetitive vomiting, lethargy, and marked pallor arose immediately after the patient was introduced with milk-based formula. Henceforth, FPIES due to cow's milk allergy was suspected. Milk and dairy products were removed from mother's diet and the infant's formula was switched from milk-based to exclusively amino acid-based formula. All symptoms disappeared within a few hours after intravenous fluid resuscitation and the patient started to gain weight. After two weeks, provocation with milk-based formula resulted in reappearance of repetitive vomiting, lethargy, and pallor, confirming FPIES. Atopy patch test with milk was positive. The patient was then recommended breastfeeding with maternal strict avoidance of milk and dairy products mixed with amino acid-based formula if required. To determine the prognosis, open oral provocation test was implemented at the age of 12 months but the test was interrupted and the patient was then admitted to the intensive care unit as a result of profuse vomiting and diarrhea. Restriction diet was continued and the patient tolerated milk at age two.

The second patient had been breastfed since the neonatal period and had complaints of failure to thrive and bloody diarrhea. He was admitted to the intensive care unit when 2,5 months old with symptoms of diarrhea, dehydration, and shock. Sepsis work-up were negative for the patient. All symptoms disappeared and the patient started to gain weight when the mother's diet was eliminated from milk and dairy products and in addition amino acid-based formula was added to infant's diet. The patient was then diagnosed with FPIES. In that period, provocation was implemented with milk-based formula and the patient developed profuse vomiting and diarrhea symptoms. Patch test for milk was negative. A milk provocation was implemented for resolution and tolerated without any problems when the patient was 15 months old.

Specific IgE and skin prick test for milk was negative for both patients.

Symptoms of classic FPIES usually begin in early infancy, within one to four weeks following introduction of cow's milk or soy protein. Studies reported that FPIES presented with symptoms within the first six months of life (5,6). Delayed introduction of cow's milk or soy in breastfed infants may result in later onset. Rarely, symptoms may begin within the first days of life as reported here. Breastfeeding is generally considered to be protective from FPIES but recently there were two case reports of infants who developed FPIES symptoms while taking only breast milk (3,4). These data suggest that not only proctocolitis but also FPIES can develop even in children who are exclusively breastfed.

However, the exact underlying mechanisms of FPIES are not clearly understood. It is postulated that ingestion of food allergens causes local inflammation mediated by T cells, leading to increased intestinal permeability and fluid shift (7). Activated peripheral blood mononuclear cells, increased tumor necrosis factor-alpha (TNF-alpha), and decreased expression of transforming growth factor-beta (TGF-beta) receptors in the intestinal mucosa may be involved in the intestinal inflammation (7, 8).

Diagnosis of FPIES through breast milk is not easy. The disease is quite rare and symptoms are vague, not striking and not well defined, at least in the milder forms. In our two cases, the diagnosis was made based on a two-week cow's milk elimination from mother's diet, followed by a supervised oral food challenge as suggested by guidelines (1). It is reported that specific IgE to cow's milk may be present in 4-25% of FPIES patients but specific IgE measurement and skin prick test were negative in our patients.

A diagnosis of FPIES should be kept in mind in infants who had severe gastrointestinal symptoms when other common etiologic factors could not be displayed. The diagnosis must be suspected even when the infant is exclusively breastfed. When specific IgE and skin tests are inconclusive, restriction diet followed by a careful oral provocation test may help the diagnosis.

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