



# INTERLEUKIN USE FOR DIAGNOSIS AND FOLLOW UP IN FOOD ALLERGIES: A CASE

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**Introduction:** Food allergy (FA) is an immune response to food proteins controlled by immunoglobulin E (IgE), cells or both (1). It affects close to 6% of children (2). Diagnostic methods might prove insufficient or inappropriate. Definitive diagnosis implies a "food challenge" that could be dangerous in patients who are prone to anaphylactic shock (3). Additionally, the challenge must be done when the patient has complied with treatment time to observe if there is oral tolerance (3). In food allergies, a prevalence in the response of T helper lymphocytes type 2 (Th2), led by interleukins (IL) and by the thymic stromal lymphopoietin (TSLP) has been stated. As such, an increase in IL-5, IL-1, IL-3, IL-4 and IL-13 could reflect the subjacent inflammatory process (4). When diagnosis is difficult, for example, if there is hematochezia during the first hours or months after birth, the measure of specific IgE is not useful and a colonoscopy is invasive. In these cases, measuring serum IL could work because an increase in IL-5 in the eosinophilic proctocolitis has been observed (5). It is also useful to assess them to define the time for the food challenge after finishing treatment (6). In pediatrics, there are few studies on IL and their correlation with the clinical expression of the allergy. IL could be established as diagnostic and follow up tests to avoid invasive and costly methods and direct the duration of the treatment. Nowadays, Colombia leads the first study that measures IL (MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel) in children with suspicion of or confirmed food allergy, and is in its processing stage. The interest of the article is to show a food allergy case in which IL would have facilitated diagnosis and follow up.

**Case report:** A two-month old girl with persistent crying since eight days after birth, for more than three hours per day, associated with day irritability, food rejection, rumination, dyschezia and meteorism. At one month, she presented rectorrhagia, reason why CMPA was considered and a restricted CMP diet for the mother and extensively hydrolyzed formula (EHF) were indicated. Pediatric gastroenterology was consulted because crying and irritability persisted, along with six bowel movements per day, Bristol type 6-7, mucus and rectorrhagia. Chronic malnutrition with decompensation was diagnosed. Symptoms and antecedents were suggestive of FA, with proctocolitis and colic. A restrictive diet was prescribed for the mother, ranitidine was maintained and an upper and lower gastrointestinal endoscopy was suggested. An IL sample was taken. A week later, the girl presented food rejection, crying when eating, occasional dysphagia, a decrease in rumination and irritability. Her height improved according to her age. At two months, there was a great improvement of gastrointestinal symptomatology, with an episode of rectorrhagia after food transgression by the mother. A week later, due to a reoccurrence of rectorrhagia, the restriction to the eight main allergens was broadened for the mother, amino acid-based formula (AAF) was started and the order to breastfeed again in two weeks was issued. An upper gastrointestinal endoscopy and a colonoscopy were insisted upon, and food-specific IgE were ordered. At three months of age, she had appetite changes, 50% decrease in crying, occasional hiccups, gesticulations, cough, 2-3 bowel movements per day, Bristol type 6. Due to persistent GI symptoms and an alteration in her nutritional status, endoscopic and specific IgE samples were insisted upon. At three months, her general status improved and crying decreased by 75%. When breastfeeding was started again, there was a reoccurrence of rectorrhagia, so it was stopped and AAF reinserted. Three days before consult, she had dermatitis on the thorax and face, along with occasional regurgitation. Her nutritional status was still affected, so endoscopies were recommended. At four months, she was assessed by pediatric gastroenterology at another institution, domperidone was started, the AAF brand was changed and a complementary diet was instated, after which her gastrointestinal symptoms and her dermatitis worsened, and cryptitis and constipation appeared. She was still underweight but with normal height. Her allergy "was not controlled" and eosinophilic esophagitis and enteropathy were suspected, so there was an emphasis on the endoscopic study. She continued to use AAF, and stopping the complementary diet was suggested. At five months, the results of the endoscopies were brought in and had findings suggestive of allergic enteropathy (AE). She was using AAF, ranitidine and domperidone. Her complementary diet was continued due to an order from another institution. She still had dermatitis, liquid bowel movements and perianal erythema. AE was considered, stopping the complementary diet was emphasized and oral prednisone was started. Other studies to rule out other malabsorption causes were ordered. At six months, she improved her general status and the consistency of her bowel movements, she had occasional episodes of abdominal distension and meteorism. A reduction of steroids was programmed and ranitidine was stopped. Directed complementary diet was resumed, other studies on malabsorption were insisted upon and an assessment by genetics was requested.



At nine months of age, she had a better general status, low intake, normal bowel movements, and perioral dermatitis with some tested foods. Metabolic acidosis was documented and a pediatric nephrology consult was requested to discard renal tubular acidosis (RTA). When she was 10 months old, she had a stable evolution from the gastrointestinal point of view. Pediatric nephrology repeated gas tests and discarded RTA. Inadequate weight gain persisted. Differential diagnosis was pending.

**Discussion:** To increase diagnostic accuracy of food allergies the medical history, physical exam, response to elimination diet and, in some cases, skin prick testing (SPT), specific IgE measurements, endoscopic procedures and challenges are useful (7). However, each one of them has its own limitations. Thus, we propose other tests like measuring IL. This patient had a high suspicion of non-IgE mediated food allergy requiring various medical interventions to confirm her diagnosis. ImmunoCAP and SPT were not useful (they came back negative). Exclusive AAF stopped the rectorrhagia but did not improve weight, requiring the study of other causes for stunted growth. Another obstacle was that her parents did not agree to endoscopic procedures. Given this, measuring IL would have been very useful to confirm her diagnosis, direct treatment, decrease complications (persistent rectorrhagia, anemia, sensitivity to other allergens, and a more compromised nutritional status) and costs. Currently, we are waiting for IL results at the beginning and during follow up.

If IL measuring were more accessible when there is suspicion of a food allergy, when finding some of them elevated, we would confirm the diagnosis. According to the literature, the levels of some cytokines have been highlighted as inflammation, improvement and response to treatment markers.

IL-10 is an anti-inflammatory cytokine that can regulate cell immunity and inflammation, and which participates in intestinal homeostasis and induction of oral tolerance (8). Chen et al. found low levels of IL-10 in non-IgE mediated food allergies compared with controls. Bartuzi et al. evaluated IL profiles in patients with food allergy and chronic gastritis, observing that chronic exposure to the allergen conditioned the increase in IL-4 and IL-5 (8,9). Semeniuk et al. showed that IL-4 and TNF- $\alpha$  were more elevated in children with gastroesophageal reflux disease (GERD) secondary to food allergies and in children with CMPA compared to children with GERD, with a decrease of both parameters in the three groups when instating treatment (10). In this case, if during the first examination serum IL could have been measured, additional tests and consults with other specialists would not have been necessary to confirm the diagnosis. All of this increased costs and anguish and impacted quality of life. Moreover, during follow up, they would have allowed for the detection of the failure in the treatment, facilitating the move toward coadjuvant treatment. On the contrary, if IL had been negative, additional laboratories would have been ordered for the differential diagnosis, and the restrictive diet for the mother, which is expensive to plan for nutritionists and hard to comply with for the mother, the cost of AAF and her exposure to systemic steroid treatment, which has important adverse effects, would have been avoided.

Hartog et al. measured IL in colon biopsies from patients with food allergies: in patients with specialized formula, there was a significant reduction in IL-6, improvement of the mucous membrane and an increase in IL-12, which direct the response to Th1 (11). These findings support the usefulness of measuring IL to continue and evaluate treatment in patients with food allergies. Summarizing, finding elevated IL could help to confirm a food allergy, especially in non-IgE mediated food allergies or with a mixed mechanism. This type of food allergy expression generally requires endoscopic studies to corroborate or discard. Nevertheless, endoscopies are not always feasible. Taking into account all of the above, measuring IL would be a less invasive, less risky, more cost-effective option to support diagnosis and follow up and to define the precise moment for the challenge.

#### Conclusions:

- IL could constitute an accurate method to diagnose and follow up food allergies, independent of the immunological mechanism involved.
- IL would help to know if the patient is close to oral tolerance and, as such, to define the food challenge, minimizing risks and easing the minds of the family and the multidisciplinary team.

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