

# Non-IgE mediated food allergy development after liver transplantation?

## Abstract

**Background:** The acquisition of new-onset food allergy after organ transplantation or transplant-acquired food allergy (TAFA) has been usually reported in adults and rarely in children. TAFA is described mainly after solid organ (e.g., liver, intestine, pancreas, kidney, lung and heart) or cord blood transplantations. In various reported studies, the male/female ratio seems to be equal. And literature data suggest that children with TAFA typically present within the first year after solid organ transplantation and they are typically allergic to multiple foods.

**Aim:** TAFA is generally characterized with allergy to multiple foods and increased level of total and/or specific IgE. Here, a patient with TAFA who had normal total and specific IgE test results plus minimal reaction to skin prick test for cow's milk is presented and his clinical presentation is discussed.

**Case Presentation:** 15 month-old boy came to our allergy clinic with complaints of vomiting after drinking cow's milk and skin rash on the area where contacted with chocolate. In his past medical history: Extrahepatic biliary atresia was diagnosed at 3 weeks age with conjugated hyperbilirubinemia (according to scintigraphy and biopsy results). Left lateral segment of liver (donor was his mother) was transplanted to him when he was at 5 months. The liver donor was not recorded as having a history of allergic disease. Methylprednisolone and tacrolimus immunosuppression were used after the transplantation, and tacrolimus therapy was continued for prophylaxis of chronic rejection. When he was at 7 months, family fed the patient with cow's milk but 3 hours later he began to vomit. He vomited five times in two hours. Then, he developed constipation. Rectal irrigation was used. Then oral intake stopped for two days. He was thought to be having food protein induced enterocolitis. His vomiting complaints repeated after intake of formula and baby food which includes grain. So he fed with special formula including short-chain peptides and free aminoacids and his symptoms improved. Family history: His father has penicillin allergy and his aunt has asthma. Physical examination revealed normal examination findings. Height and weight were within normal percentiles. Laboratory findings: WBC was 4.420/mm<sup>3</sup>, with 21% neutrophils, 6% eosinophils and 69% lymphocytes. His hemoglobin was 8.2 g/dl, platelet count was 280.000/mm<sup>3</sup>. Total IgE : <5 and ImmunoCAP specific IgE against milk, grain and other six classic foods was <0.35. Skin prick test results: saline: 0x0mm, histamine 4x4mm, Fresh cow's milk: 2x2mm, other food allergens (peanut, egg, fish, soybean, wheat): 0x0mm.

**Conclusion:** Our patient seemed to have TAFA, cow's milk allergy with gastrointestinal manifestations (FPIES), after liver transplantation. Transplant-acquired new allergy needs to be considered after solid organ transplantation, especially when tacrolimus is used as immunosuppressive agent.

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**Abbreviations:** FPIES: Food Protein-Induced Enterocolitis Syndrome; TAFA: Transplant-Acquired Food Allergy

## Background

The acquisition of new-onset food allergy after organ transplantation or transplant-acquired food allergy (TAFA) has been usually reported in adults and rarely in children.<sup>1</sup> TAFA is described mainly after solid organ (e.g., liver, intestine, pancreas, kidney, lung and heart) or cord blood transplantations.<sup>2,3</sup> In various reported studies, the male/female ratio looks equal. And literature data suggest that children with TAFA typically present within the first year after solid organ transplantation and they are typically allergic to multiple foods.<sup>3</sup> The pathogenesis of TAFA is not still completely known. Increasing data support the concept that the functioning liver itself, in addition to tacrolimus immunosuppression, is one of the main contributors to TAFA in these patients. In the light of recent literature findings, further possible mechanisms might be summarized as following:

- i. Late manifestation of food allergy;
- ii. Intestinal injury with inhibition of cellular energy production by tacrolimus; and
- iii. Passive transfer of food-specific IgE or lymphocytes from the donor. Thus, interaction between hematopoietic stem cells of the donor and recipient (host)'s specific factors (e.g. being atopic and younger age) appear to underlie in the development of TAFA.<sup>1,4-6</sup>

For instance: Boyle et al.<sup>7</sup> reported a case indicating that host-specific factors play an important role in the TAFA after liver transplantation, and emphasizing the predisposition that children have headed for this phenomenon. Accordingly, they observed TAFA development in a child who received a split liver graft. This case is amazing for the absence of TAFA development in the adult recipient of the same split liver graft. They conclude that host factors such as the maturity of immune regulatory mechanisms, especially in children, are thought to play a significant role in the development of TAFA after liver transplantation.

## Aim

TAFAs are generally characterized with allergy to multiple foods and increased level of total and/or specific IgE. Here, a patient with TAFAs who had normal total and specific IgE test results plus minimal reaction to skin prick test for cow's milk is presented and his clinical presentation is discussed.

## Case presentation

15 month-old boy came to our allergy clinic with complaints of vomiting after drinking cow's milk and skin rash on the area where contacted with chocolate. In his past medical history: Extrahepatic biliary atresia was diagnosed at 3 weeks age due to prolonged conjugated hyperbilirubinemia (according to scintigraphy and biopsy results). He went thru left lateral segment transplantation of liver (donor was his mother) when he was at 5 months of age. The liver donor was not recorded as having a history of allergic disease. Methylprednisolone and tacrolimus immunosuppression were used after the transplantation, and tacrolimus therapy was continued for prophylaxis of chronic rejection. When he was at 7 months, family fed the patient with cow's milk but 3 hours later he began to vomit. He vomited profusely five times for two hours. Then, he developed constipation. Rectal irrigation was used. Then oral intake stopped for two days. He was thought to be having food protein-induced enterocolitis (FPIES). His vomiting complaints repeated after intake of formula and baby food which includes grain. After he was fed with special formula including short-chain peptides and free aminoacids, his symptoms improved. Family history: His father has penicillin allergy and his aunt has asthma. Physical examination revealed normal examination findings. Height and weight were within normal percentiles. Laboratory findings: WBC was 4.420/mm<sup>3</sup>, with differentials of 25% neutrophils, 6% eosinophils and 69% lymphocytes. Hemoglobin was 8.2g/dl, platelet count was 280.000/mm<sup>3</sup>. Total IgE:<5 and ImmunoCAP specific IgE against milk, grain and other classic 6 foods was <0.35. Skin prick test results: saline: 0x0mm, histamine 4x4 mm, fresh cow's milk: 2x2mm, other food allergens (peanut, egg, fish, soybean, wheat): 0x0mm.

## Discussion

Although laboratory investigations and clinical presentation of the patient did not look like typical IgE-mediated food allergy, our patient seemed to develop TAFAs related to liver transplantation. Different clinical presentations of TAFAs have been recently defined.<sup>4</sup> New-onset TAFAs, whether immediate (IgE-) hypersensitivity type or non IgE-type (e.g., eosinophilic gastroenteropathy), is an infrequent but potentially severe complication of organ transplantation. Eosinophilic gastroenteropathy is frequent after transplantation and should be considered in all recipient children with gastrointestinal symptoms undergoing transplantation. Our patient was thought to be experiencing FPIES. To our best of knowledge, FPIES, as a manifestation of TAFAs, has not been reported before. FPIES is an uncommon and potentially severe type of non-IgE-mediated gastrointestinal food allergy. It is characterized by repeated and delayed (1-3 hours) vomiting and/or diarrhea with (out) lethargy due to dehydration and shock following exposure to the culprit food and no other explanation for the symptoms.<sup>8</sup> Most patients get symptomatic improvement following reduced immunosuppression and an appropriately restricted diet. Similarly, as in our patient, they mostly respond well to special formula including short-chain peptides and free aminoacids as well.

Some of recent studies report the long-term outcome of TAFAs development in this population. Although most of food sensitivities

are known to be lost, some children remain food allergic for a long period of time. Mavroudi et al.<sup>9</sup> reported 3 cases that the symptoms of food allergy persisted for 8 years in their first case and for 2 years in the other two cases. The long term prognosis in their cases was excellent and food allergy resolved in all the patients. Moreover, some studies show that in long term allergic diseases may occur in some of pediatric solid organ transplant recipients, with manifestations including atopic dermatitis, allergic rhinitis, and asthma.<sup>4</sup> Shroff et al.<sup>10</sup> observed liver transplanted 176 pediatric recipients for manifestations of allergic disease. They shown that atopy occurs in approximately 14% of recipients. Frischmeyer-Guerrero et al.<sup>11</sup> reviewed retrospectively 25 patients with TAFAs and demonstrated that allergic rhinitis seen in 11/25; eczema in 11/25 and asthma in 8 out of 25 transplant recipients. In near future, further studies are necessary to determine whether TAFAs are transient or not in pediatric and adult after solid organ transplantations. Thus, transplant recipient patients might be needed to be followed-up for long term.

Our patient seemed to have TAFAs, cow's milk allergy with gastrointestinal manifestations (FPIES), after liver transplantation. Transplant-acquired new allergy development needs to be considered after solid organ transplantation, especially when tacrolimus is used as an immunosuppressant. The practicing allergy-immunology and transplantation specialists keep in mind that different presentations of TAFAs in short as well as long-term may occur after solid organ transplantation.

In conclusion: Understanding the development of transplant-acquired new allergies helps improve transplanted patient management and provide more insights into new allergy development following transplantations. Further studies are indispensable to describe this novel complication as well as counseling of transplanted patients after liver transplantation would be important.

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## Conflicts of Interest

There is no conflict of interest.

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