

De Novo Food Allergy in Pediatric Recipients of Liver Transplant

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Abstract

Allergic and atopic conditions, including food allergy, asthma, eczema and eosinophilic disease of the gastrointestinal tract after liver transplant in previously non-allergic children have been increasingly described. After a liver transplant, children can present mild to severe reactions to food allergens (i.e., from urticaria-angioedema to life-threatening anaphylactic reactions). *De novo* post-transplant food allergy may become clinically evident in children who undergo liver transplant between a few months and a few years of transplant. The present narrative review aims to describe the spectrum of *de novo* post-transplant food allergy development, the current theories of pathogenesis, risk factors and to suggest possible clinical management strategies.

Keywords: Liver; transplant; food; allergy; anaphylaxis

Learning points

- Food allergies are immune-mediated hypersensitivity responses to food proteins;
- About 50% of *de novo* post-transplant food allergies develop in the first six months after liver transplant;
- Recipients can present mild to severe immunoglobulin E-mediated reactions to food allergens (i.e., from urticaria-angioedema to life-threatening anaphylactic reactions);

- Eosinophilic disorders are frequently described in patients developing post-transplant food allergies;
- The elimination diet is still the cornerstone of the management strategy of post-transplant food allergies;
- Pharmacologic treatments (e.g., epinephrine, corticosteroids, antihistamines, proton pumps inhibitors) are used as standard treatments for food allergies in association with the elimination diet
- Discontinuation of tacrolimus with the therapeutic switch to cyclosporin or sirolimus and/or the combination therapy with mycophenolate mofetil could be effective for resolution of food allergies

Introduction

Allergic and atopic conditions, including food allergy, asthma, eczema and eosinophilic disease of the gastrointestinal tract, after organ or stem cell transplant in previously non-allergic recipients have been increasingly described. *De novo* post-transplant food allergy (*dnPTFA*) was reported for the first time in 1997 following a combined liver and kidney transplant to a 35-year-old man⁽¹⁾ and in a 17-month-old liver transplanted child who presented severe allergic reactions following ingestion of cow's milk⁽²⁾. Since these initial reports, there have been subsequent case reports and series of children and adults developing food allergies after organ or stem cell transplant from donors with or without documented history of previous food allergy. The present narrative review aims to describe the spectrum of *dnPTFA* development, the current theories of pathogenesis, risk factors and to suggest possible clinical management strategies.

Methods

We undertook a comprehensive narrative literature review using PubMed to identify key studies on pediatric liver transplant and food allergies in the following areas: epidemiology, pathophysiology, risk factors, clinical presentation, diagnosis and treatment. A formal, quantitative systematic review was not considered appropriate for this comprehensive review.

Prevalence

The reported prevalence of food allergy after liver transplant in children is between 5% ⁽³⁾ and 40% ⁽⁴⁻¹²⁾. The estimates across the different studies varied due to the heterogeneous diagnostic criteria used (from self-reporting to more complex diagnostic approaches including clinical symptoms and laboratory evaluations) and the different duration of follow-up of the studies.

Pathophysiology

Food allergies are immune-mediated hypersensitivity responses to food proteins. There are multiple proposed mechanisms for the pathogenesis of *dnPTFA*. *DnPTFA* can develop by passive transfer of donor immunoglobulin (Ig) E or lymphocytes. This mechanism is unlikely to account for the large number of *dnPTFA* cases occurring more than six months after transplant. More importantly, recipients, especially those who are young and have not been in contact with some food allergens before liver transplant (because of restrictive diets in metabolic liver disease or due to the use extensively protein hydrolysate formulas), may develop *dnPTFA* as a lack acquisition of tolerance when exposed to a “new” food antigen in the non-tolerogenic post-transplant setting. Furthermore, loss of tolerance to food allergens after transplant have been accounted for in the pathophysiology of *dnPTFA*.

Risk factors

Different risk factors have been associated with the development of *dnPTFA*, and the following have been described in multiple studies: age at transplant, types of immunosuppressive therapy and of transplanted organ and Epstein-Barr virus (EBV) infection.

Age at transplant

The younger the recipient is, the higher is the risk of *dnPTFA*. Infants and children younger than two years ^(13, 14) are at high risk of *dnPTFA*. Indeed, this is particularly true for the development of food allergy, while the prevalence of other post-transplant allergic diseases is independent of age and similar for children and adults ⁽¹⁵⁾. Also, the young age of the donor seems to impact the risk of *dnPTFA* in the recipient ⁽⁷⁾.

Immunosuppressive therapy

Calcineurin inhibitors (CI, e.g., cyclosporine, tacrolimus) have been implicated and identified as a potentially modifiable risk factor for *dnPTFA*. Tacrolimus and, with a lower potency, cyclosporin impair the functioning of Treg cells ^(16–18), inhibit the production of interleukin-2, decrease interleukin-10 ⁽¹⁹⁾ and increase interleukin-5. With this immunologic imbalance, when an antigen-presenting cell encounters a food antigen and presents it to a naïve T cell, the imbalanced immunity results in a Th2 response ^(20, 21) instead of a Treg cell response, in the suppression of the T-helper cell responses, particularly Th1 and in the production of IgE and activation of mast cells and eosinophils. Furthermore, CI increase intestinal permeability, which may, in turn, increase allergen exposure through the gut ^(7, 22–26). Eosinophilia is frequently detected in children who have developed *de novo* food allergy while on CI. Eosinophils can be considered to be markers of, rather than risk factors for new-onset food allergy ^(26, 27).

Tacrolimus is the cornerstone of immunosuppressive treatment after liver transplant. Tacrolimus is used less frequently in bone marrow transplant compared with solid organ transplant and patients undergoing non-liver solid organ transplant more frequently receive

combined therapy with tacrolimus and steroids or mycophenolate mofetil. Mycophenolate mofetil is a known suppressor of B-lymphocyte activity and reduces IgE production.

Bone marrow, liver and other solid organs transplant

DnPTFA has been observed more frequently following liver transplant than following non-liver solid organ (e.g., heart, lung, intestine, kidney and pancreas) transplant and bone marrow transplant. De Bruyne et al. compared 49 children who underwent liver transplant with 21 who received kidney transplant. *DnPTFA* occurred in 13 and none of the children who received a liver transplant and a kidney transplant, respectively⁽⁷⁾.

Several mechanisms may help to explain the different frequency of food allergies after solid organs and bone marrow transplant. First, liver and other organs such as small bowel harbour lymphoid tissue and specifically food-specific Th2 lymphocytes and/or B lymphocytes that may promote or temporally produce IgE antibodies in the recipient following organ transfer. Second, the liver has a critical role in development of tolerance to food antigens and autoantigens. After liver transplant the intestinal mucosa integrity is disrupted as a consequence of the use of tacrolimus and of viral infections and the intestinal flora is altered due to antibiotic treatment and the presence of hepaticojejunostomy after split liver in young children. Finally, the post-transplant immunosuppressive treatment regimen that could be based in most liver transplant recipients on the use of tacrolimus alone or on tacrolimus with steroids and/or mycophenolate mofetil and other drugs, as described above, could influence the risk of *dnPTFA* development. Mycophenolate mofetil is an immunosuppressive drug given particularly to kidney transplant patients and this may help explain why food allergy is more common in liver as compared to kidney recipients.

All these conditions may contribute in the short and in the long-term to the increased risk of *dnPTFA* after liver transplant.

Epstein-Barr virus infection

EBV infection has been suspected in some but not all studies, of being involved in the development of *dnPTFA*^(4, 28). EBV may influence the immune system to create a predominant Th2 activity with less cytotoxic T lymphocyte control, which increases the risk of atopy and allergy. However, the association of EBV with food allergy may reflect a state of overimmunosuppression with CI inhibitors.

Other risk factors

Other risk factors for food allergy development have been studied so far with conflicting results. In particular, ethnicity or genetic factors are suspected to influence food allergy development, but no convincing evidence or results have been obtained⁽²⁹⁾. The hypothesis that genetic factors could impact the development of *dnPTFA* seems reliable because the atopic status of the donor and that of the recipient (with a positive family history of atopic disease) are associated with a high risk for *dnPTFA*^(4, 30, 31) even if not all the studies on the

subject confirm this association ⁽¹⁰⁾. Conflicting evidence also exists regarding the role of gender, with a few studies identifying female gender as a risk factor for *dnPTFA* ^(4, 31, 32). A few authors have analyzed the severity of liver failure before liver transplant as a possible risk factor for food allergy development ⁽³⁰⁾. In particular, food sensitization pre-transplant seems to occur in young children with severe liver dysfunction ^(33, 34). Recently, the diagnosis of atopic dermatitis ⁽³²⁾ and asthma ⁽³⁵⁾ in the recipient has been associated with the development of *dnPTFA*. The most frequent food allergens associated with asthma in transplanted children are milk, eggs and peanuts ⁽³⁵⁾. Finally, rejection episodes ⁽³⁶⁾, the development of post-transplant lymphoproliferative diseases ⁽¹⁰⁾ or the presence of autoantibodies ⁽³⁷⁾ have been evaluated as possible risk factors for *dnPTFA*.

Time matters: clinical onset

DnPTFA may become clinically evident in the majority of children who undergo liver transplant between a few months and a few years of transplant. Previous studies have demonstrated that about half of *dnPTFA* develops in the first six months after liver transplant ^(10, 38), but the diagnosis of *dnPTFA* could be as late as eight years after transplant ⁽¹³⁾. The variability in the timing of the diagnosis can be secondary to the retrospective nature of most of the studies published so far and by the low number of children in whom *dnPTFA* has been confirmed by oral provocation test with the difficulty of discriminating between sensitization (positive skin prick tests or food-specific IgE) and food allergy (clinical manifestations occurring with the food intake). Furthermore, in clinical terms, the signs and symptoms of *dnPTFA* could be mild, subtle and unclear, accounting for the longer latency from transplant to the final diagnosis ⁽¹³⁾.

Clinical manifestations

After a liver transplant, recipients can present mild to severe reactions to food allergens. *DnPTFA* can present clinically as angioedema or urticaria, eczema, asthma, allergic rhinitis, diarrhoea, growth failure and life-threatening anaphylactic reactions ^(39–41). Table A, provided as supplementary file, <http://links.lww.com/MPG/C569>, provided as supplementary file, summarizes the most common clinical manifestations and the most frequently involved allergens. Cutaneous and gastrointestinal signs and symptoms are the most commonly described. Isolated gastrointestinal clinical manifestations may be secondary to eosinophilic gastrointestinal disease whose diagnostic hallmarks are the eosinophilic infiltrates on biopsies. In this case, gastrointestinal signs and symptoms are not secondary to IgE-mediated reactions and therefore not associated with a risk of immediate reactions. Eosinophilic gastrointestinal disease in children who underwent a liver transplant is up to 100 times more frequent than in non-transplanted children. ^(5, 13)

Foods most frequently involved in allergic reactions

The most common food allergies described after a transplant are similar to those presented by non-transplanted children and include milk, egg, wheat, peanuts and nuts in general, fish, soy and, less frequently, fresh fruits such as peaches.

Outcomes of post-transplant food allergies

Gradual age-related resolution of non-transplanted-related food allergy is reported in the literature from 2% after the first year of life to 78.6% after the sixth year of life ⁽⁴²⁾. Overall, two types of *dnPTFA* have been identified: transient and persistent ⁽³⁷⁾. Transient *dnPTFA* can be due to the transfer of specific IgE from the donor. It usually develops within two months of the transplant and resolves in the first year ⁽³³⁾. Persistent *dnPTFA* is more likely to develop remotely from the transplant ⁽⁴³⁾. Studies describing the long-term outcome of food allergy in children demonstrated that most children remain sensitized to at least a subset of foods for an extended period. Studies on solid organ transplant recipients suggest that at least 12% of patients will outgrow their food allergies after six years ⁽³⁸⁾. In the study by Wisniewski J et al., 10 of 24 children who underwent a liver transplant were on an unrestricted diet 10 years after the transplant ⁽¹³⁾.

Several studies have shown that older recipients have had more chance to outgrow their allergies than younger children ⁽¹⁵⁾. Table A, provided as supplementary file, <http://links.lww.com/MPG/C569>, summarizes the prognosis of *de novo* food allergies after liver transplant.

Management

The management of children with *dnPTFA* is based on a few, simple but major indications. In the specific case of living related liver transplant, it is recommended to screen the donor before transplant for food allergy and atopy. When the donor is diagnosed with food allergy, the recipient should be tested within the first months of transplant for the presence of food-specific IgE, and it is advisable to introduce the suspected food in a controlled setting. The half-life of IgE in plasma is estimated to be 2-3 days ⁽⁴⁴⁾. For this reason, it could be advisable not to dose specific IgE before 7 days from liver transplant not to detect donor antibodies.

It has been suggested that careful feeding based on hypoallergenic foods, in particular with the avoidance of the so called “big eight allergens” (milk, eggs, peanuts, tree nuts, fish, shellfish, wheat and soy) and progressive introduction of allergens in young children who were on restrictive diets before transplant may be indicated in recipients at high risk of *dnPTFA*.

Recipients and their families should be taught to recognize the signs and symptoms of food allergy. In case of the development of clinical manifestations of food allergy after liver transplant, the elimination diet of the allergen is recommended, and when an IgE-mediated allergy is suspected, auto-injectable epinephrine should be prescribed ⁽⁴³⁾. Other specific

treatments such as corticosteroids and antihistamines are indicated ^(45, 46). When *dnPTFA* presents as eosinophilic gastrointestinal disease, several drugs, e.g., proton pump inhibitors and corticosteroids can be useful in resolving the associated clinical manifestations ^(47, 48). The management of eosinophilic gastrointestinal diseases, especially concerning eosinophilic esophagitis, is based on elemental diets (the most restrictive of elimination diets removing all possible food allergens) or on empiric elimination diets removing a subset of food antigens most commonly reported associated with the diseases or and food allergies (milk, egg, wheat, soy, peanuts, tree nuts, fish, or legumes). They may be used as an exclusive approach or in combination with pharmacological treatment⁽⁴⁹⁾.

Several ^(50, 51) but not all studies ^(8, 27, 52) support how switching from tacrolimus to cyclosporine or adding mycophenolate mofetil to suppress B-lymphocyte activity and reduce IgE production could improve the efficacy of the elimination diet and favour the resolution of *dnPTFA*. During the decision-making process of whether or not to switch from tacrolimus to cyclosporine (a less powerful immunosuppressant), the potential risk for organ rejection should be taken into account ⁽²⁶⁾. Furthermore, recent reports showed the beneficial effects of switching from tacrolimus to sirolimus. Due to its antiproliferative effects, sirolimus effectively resolved autoimmune post-transplant cytopenia and post-transplant acquired lymphoproliferative disorders. Moreover, it inhibited antibodies production^(4, 47).

The elimination diet is considered the most effective measure for children with *dnPTFA*. After the-beginning of the-elimination diet, total and specific IgE levels, in combination with skin prick tests, are essential for establishing when a food provocation test can be safely performed to prove IgE-mediated food allergy outgrow ⁽²⁹⁾. Monitoring for peripheral blood eosinophils (even considered a marker with low sensitivity/specificity), local tissue eosinophilic infiltrates (as a marker of disease activity and inflammation) are crucial in eosinophilic gastrointestinal diseases⁽⁵³⁾. During the elimination diet, the immunosuppressant serum level should be monitored and the dose should be decreased frequently, due to the impact of food allergies on mucosal immunity with alteration of the gastrointestinal barrier affecting absorption and bioavailability of immunosuppressive drugs ⁽¹⁵⁾.

No studies are available on the possible role of a new biologic drugs used to treat food allergies or on the safety and efficacy of oral immunotherapy in the course of food allergy in patients with *dnPTFA*. Figure 1 summarizes the algorithm currently used in our centre for management of *dnPTFA* according to the severity of the clinical manifestations and the presence or absence of risk factors for the persistent type.

Conclusion

The survival of transplanted children, given the advances in medical and surgical practices, is excellent.

DnPTFA is common after liver transplants in children and could present with clinically relevant and life-threatening anaphylactic reactions. Treatment options are limited, and an

early diagnosis is crucial to start the elimination diet and prevent possible contact with the food allergen. A multidisciplinary approach by hepatologists, dietitians, paediatricians, and allergologists is required to better define the risk for future reactions to food, avoid unnecessary diet, and propose active management of food allergy after discussing with parents the risks/benefits of different approaches.

Multicentre prospective studies are needed to inform the extent of these conditions after solid organ transplant and to guide its effective management.

Note: [§] in case of high level of specific IgE with persistence of specific IgE positivity over time provide instruction for caregivers and epinephrine or decide to perform an oral food challenge; ^{*} peripheral blood eosinophils count has low sensitivity and specificity; local tissue eosinophilic infiltrates are a marker of disease activity and inflammation. Do not use peripheral eosinophils count to make a decision because of their low usefulness but use them as additional information in a wider context including clinical findings, biopsies results and allergy tests results; [^] severe throat angioedema prescribe epinephrine; [°] consider risk benefit; acquire informed consent; perform oral food challenge only when history of anaphylaxis is doubtful.

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Figure 1. Algorithm for management of *de novo* post-transplant food allergy according to the severity of the clinical manifestations and the presence or absence of risk factors

