

Post-transplant food allergy in children is associated with liver and not with renal transplantation: A monocentric comparative study

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Abstract Food allergy is increasingly reported after paediatric liver transplantation. The underlying physiopathological mechanism remains incompletely understood. Therefore, we aimed to determine the incidence, clinical presentation, possible risk factors, and prognosis of post-transplant food allergy in children currently followed after liver and renal transplantation. The study population consists of 49 liver and 21 renal transplant patients transplanted between the age of 22 months and 15 years. Data were collected retrospectively from medical records and via a doctor's questionnaire taken from the parents in a monocentric setting. Post-transplant food allergy has developed in 13 liver transplant patients and in none of the renal transplant recipients. Within the liver transplant group, median age at liver transplantation is significantly lower in the food-allergic (10 months) versus non-food-allergic group (3.3 years; $p=0.002$). The use of tacrolimus as primary maintenance immunosuppression is associated with food allergy ($p=0.032$) and mean

donor age is significantly lower in the food-allergic group ($p=0.009$). Compared to the renal transplant group, median age at transplantation is significantly lower in the liver patients ($p<0.001$). No significant differences are found in primary immunosuppressive regimens between renal and liver transplant patients. **Conclusion:** Post-transplant food allergy is an important clinical problem in children after liver transplantation which does not affect renal transplant patients despite similar immunosuppressive regimens. Within the group of liver transplant recipients, tacrolimus use, young age at time of transplant and younger donor age were associated with the development of food allergy.

Keywords Children · Food allergy · Immunosuppression · Liver transplantation · Renal transplantation

Abbreviations

ALF	Acute liver failure
CMP	Cow's milk protein
EE	Eosinophilic oesophagitis
EHBA	Extrahepatic biliary atresia
FTT	Failure to thrive
LTx	Liver transplantation
NP	Not performed
PFIC	Progressive familial intrahepatic cholestasis
PN	Parenteral nutrition
sIgE	Specific IgE
SPT	Skin prick testing

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Introduction

Paediatric liver transplantation has evolved from an experimental procedure to a state-of-the-art therapy for acute and

chronic liver disease. Due to significant improvements in surgical techniques and immunosuppressive treatment over the last decades, actual survival data are excellent. Hence, our focus has shifted towards optimisation of quality of life and minimisation of long-term complications.

The occurrence of new onset food allergy has increasingly been reported after paediatric liver transplantation [2, 6, 9, 11–13]. To date, the underlying physiopathological mechanism is incompletely understood. Tacrolimus-based maintenance immunosuppression, frequently used in paediatric solid organ transplantation, seems to play a role by inducing a shift towards T-helper 2 cells. Eosinophilia and other allergic features are also more prevalent in other “non-liver” solid organ transplant recipients treated with tacrolimus [1]. However, food allergy is mainly seen after liver transplantation [10]. This finding suggests that tacrolimus is not the only predisposing factor in the development of food allergy and supports the role of the liver in the development of immune tolerance.

There may be some reporting bias however, as liver transplant patients are mostly followed by paediatric gastroenterologists, subspecialists with an interest in food allergy. Furthermore, other confounding factors could play a role.

By analysing in detail the characteristics of children currently followed after liver and renal transplantation in a monocentric setting, we aim to further determine the incidence, clinical presentation, possible risk factors and prognosis of post-transplant food allergy.

Patients and methods

Between 1995 and 2010, 65 and 49 children (age 0–16 years), respectively, underwent a liver or kidney transplantation at Ghent University Hospital. Our study population consists of 49 liver (median age, 10 years) and 21 kidney (median age, 15 years) organ recipients currently still under follow-up in the paediatric department. More detailed information regarding these patients is summarised in Table 1.

Informed consent was given by the parents and/or patients and after obtaining written approval, data were collected from the medical records. Via an extensive doctor’s questionnaire taken from the parents, detailed information was obtained regarding medical antecedents, family history, diet history and history of (acute onset and subacute/chronic) atopic signs and symptoms prior to and post-transplant.

The diagnosis of food allergy was based on convincing clinical signs followed by a clear response to elimination (disappearance of signs after withdrawing the food allergen from the diet) and provocation (re-occurrence of signs when food antigen is reintroduced in diet). Supervised open food challenge was performed when clinical history and clinical features were not unequivocal and/or in case of IgE-mediated acute signs.

Skin prick testing (prick to prick) was performed with fresh products according to standard guidelines [17]. Histamine chloride and sodium chloride (0.9 %) were used as positive and negative controls, respectively. Specific IgE was measured by the ImmunoCAP assay (Phadia®).

Table 1 Patient characteristics of renal and liver transplant recipients

	Liver transplant recipients	Renal transplant recipients
Patient number in follow-up	49	21
Male/female	29/20	14/7
Median (range) age at transplant	22 Months (3 weeks–16 years)	8.9 (2–15) Years
Median (range) duration follow-up	67 (19–230) Months	74 (10–166) Months
Current (range) age	10 (3–20) Years	15 (5–22) Years
Type of transplant	Living related (7) Cadaveric organ (42) Split/reduced size (31) Whole organ (11)	Living related (2) Cadaveric organ (19)
Indication	Extrahepatic biliary atresia (18) Acute liver failure (11) Inborn errors of metabolism (8) Familial intrahepatic cholestasis (3) Other (9)	Congenital nephro-uropathy (8) Inborn errors of metabolism (5) Nephronophthisis (4) Other (4)
Immunosuppression	Tacrolimus (35) Cyclosporin (14) Mycophenolate mofetil (20) Maintenance steroids (8) Sirolimus (4) Basiliximab (induction) (30)	Tacrolimus (14) Cyclosporin (7) Mycophenolate mofetil (15) Maintenance steroids (7) Sirolimus (0) Basiliximab (induction) (16)
New onset food allergy	13	0

The immunosuppressive protocol in the liver transplantation programme has evolved during the study period. Until July 2003, the protocol consisted of a perioperative bolus of 10 mg/kg methylprednisolone, followed by maintenance immunosuppression with cyclosporine (target trough concentrations of 200–250 ng/ml on the first 3 months, 150–200 ng/ml on the first year post-transplant and <150 ng/ml afterwards) and prednisolone (dosage of 2 mg/kg during 5 days, progressively tapered and discontinued after 3 months). From July 2003 on, basiliximab was added as induction immunosuppression (10/20 mg at days 0 and 4 post-transplant for children <30/≥30 kg); furthermore, cyclosporine was replaced by tacrolimus (target trough concentrations 10–12 ng/ml on the first 3 months, 8–10 ng/ml on the first year post-transplant and <8 ng/ml afterwards). Mycophenolate mofetil was associated to calcineurin inhibitors on indication (e.g. renal impairment, recurrent rejection episodes) in a dose of 600 mg/m² twice daily (max., 2 g daily). In the renal transplant programme, the immunosuppressive protocol has been similar with two minor differences. Instead of prednisolone, 30 mg/m² of prednisone is used twice daily tapered gradually after 1 week during the first 3 months with maintenance of low-dose prednisone afterwards. Furthermore, mycophenolate mofetil is associated in each renal transplant patient.

Data were analysed in SPSS Statistical package, version 19. Chi-square test was used to compare categorical variables and Mann–Whitney *U* test to compare continuous variables between groups. To evaluate independent risk factors, multiple logistic regression analysis was performed using food allergy as dependent variable and age at time of transplant, primary immunosuppression (cyclosporine versus tacrolimus) and donor age as covariates. A *p* value of <0.05 was considered statistically significant. The study has been approved by the local ethics committee of Ghent University Hospital.

Results

Thirteen of the 49 paediatric liver transplant recipients developed new onset food allergy compared to none of the children in the renal transplant group. The most frequent causative food allergens are cow's milk protein, egg, peanut and soy.

Seven of the 13 patients have multiple food allergies. IgE-mediated (signs within minutes to hours of ingestion of foods) allergic reactions were seen in 3 of 13 compared to mixed and non-IgE-mediated reactions (with delayed/subacute onset and chronic signs) in 8 of 13 and 2 of 13 patients, respectively [16]. Ten of 13 presented with gastrointestinal manifestations (diarrhoea with faltering growth, blood in stools and vomiting), other signs were angioedema, urticaria, anaphylaxis and severe atopic dermatitis. Furthermore, three patients suffer from treatment-resistant cheilitis with oral mucosal lesions (Fig. 1). One food-allergic patient was diagnosed with



Fig. 1 Treatment-resistant oral mucosal lesions in a 6-year-old boy, 5 years post-combined liver–intestinal transplantation. Angular cheilitis, pale cracked lips with zones of hyperpigmentation, nodular tongue lesions with cobblestoning, dark pigmentation of tongue mucosa

eosinophilic oesophagitis (nodular aspect of oesophageal mucosa with longitudinal fissures on endoscopy, microscopy revealed >20 eosinophils per high power field not responsive to treatment with proton pump inhibitors; Fig. 2). The patient characteristics, clinical signs and type of allergic reaction, responsible food allergens and diagnostic parameters in these patients are listed in Table 2.

In at least 9 of 13 patients, food allergy presented in the aftermath of an episode of proven viral gastroenteritis (positive antigen detection test for adeno- or rotavirus and/or positive viral stool culture). In the non-food-allergic group,

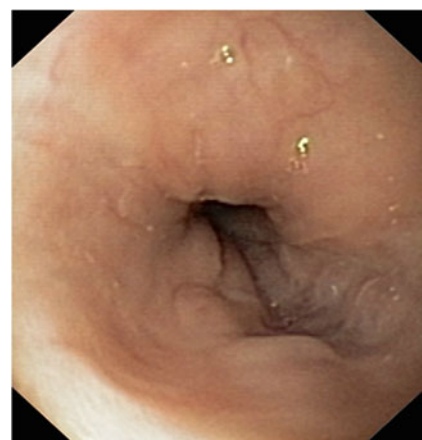


Fig. 2 Endoscopic findings in a 7-year-old girl, 6 years post-liver transplantation: pale oesophageal mucosa with nodular aspect and longitudinal ridges

Table 2 Responsible food antigens, clinical features and diagnostic parameters in food-allergic liver transplant patients

Case	Food antigen causing clinical reaction	sIgE (kU/l)	SPT (mm) ^a	Type of allergic reaction	Signs	Indication LTx	Age at LTx/diagnosis interval FA ^b (months)	Other allergy
1	CMP	0.65 (0–0.1)	11	Mixed	Diarrhoea	EHBA	6.4 2	Eczema (resolved)
2	Peanut	2.44 (0–0.35)	NP	Mixed	Angio-oedema, diarrhoea	PFIC	5.1 6	Allergic rhinitis, eczema
3	Hen's egg (white)	6.05 (0–0.35)						
3	Hen's egg	NP	7	Mixed	Angio-oedema, urticaria, diarrhoea	EHBA	10.1 13	–
3	Soy	NP	5					
4	Hen's egg (yolk/white)	1.75 (0–0.35)/3.36 (0–0.1)	6	Mixed	Diarrhoea, FTT	EHBA	22.7	–
	CMP	53 (0–0.35)					8	
5	CMP	Negative	Negative	Non-IgE mediated	Watery diarrhoea	Tyrosinaemia type 1	35.8 2	Eczema
6	Hen's egg (yolk/white)	NP	8/9	Mixed	Angio-oedema, chronic cheilitis	PN induced liver disease	8.3 7	Eczema
7	Hen's egg	3.05 (0–0.35)	NP	Mixed	Blood in stools, anaemia	EHBA	10.6 9	–
	Banana	1.05 (0–0.1)						
	Avocado	2.45 (0–0.1)						
8	Hen's egg ^c	1.35 (0–0.35)	NP	IgE mediated	Anaphylaxis	ALF	10.1 10	–
9	Peanut	0.93 (0–0.35)	NP	IgE mediated	Angio-oedema	EHBA	10.3 12	Eczema
10	Soy, CMP, kiwi, banana, chicken, apple	NP	Banana 5, Other foods negative	Mixed	Blood in stools, chronic diarrhoea, FTT	Neonatal hemochromatosis	0.7 5	–
11	Soy, CMP, wheat, apple	Negative	Negative	Non-IgE mediated	Diarrhoea, severe FTT, chronic cheilitis	EHBA	15.3 1	–
12	Hen's egg (yolk/white)	1.55 (0–0.1)	Negative	Mixed	Diarrhoea, EO, chronic cheilitis, FTT	ALF	5.3 24	Eczema
	CMP	8.02 (0–0.35)	12					
		2.15 (0–0.35)	NP					
13	Peanut	3 (0–0.35)	NP	IgE mediated	Angio-oedema, acute vomiting	EHBA	48 22	–
	Crustacea	2.7 (0–0.35)						

^aHighest mean diameter value of wheal (in millimeter)^bTime interval in months between liver transplantation and diagnosis food allergy^cPatient has outgrown food allergy

2 of 36 children have asthma or allergic rhinitis and 7 of 36 atopic dermatitis. Hence, in total, 21 of 49 patients present atopic disease after liver transplantation. In all but one, atopy had its onset after transplantation (one patient had allergic rhinitis prior to transplant).

Food allergy was diagnosed after a median time interval of 8 (1–48) months post-transplant. The median follow-up since diagnosis of food allergy is 72 (33–188) months. In terms of prognosis, only 1 in 13 children has outgrown the food allergy. In the renal transplant group, two patients have eczema and none of them have food allergy, allergic rhinitis or asthma.

Food-allergic versus non-food-allergic liver transplant patients

Median age at liver transplantation is significantly lower in the food-allergic (10 months; range, 3 weeks–2.9 year) versus non-food-allergic group (3.3 year; range, 1 month–16 year; $p=0.002$). The use of tacrolimus as primary maintenance immunosuppression (opposed to cyclosporine) is associated with food allergy ($p=0.032$). When comparing donor age, a significant difference is found with the mean donor age in the food-allergic group being significantly lower ($p=0.009$).

No statistical correlation is found with positive familial history for food or other atopic disorders in first grade relatives. None of the living related donors (5) has a clinical history of food allergy, where two in five of these recipients developed food allergy. Data on allergy were not available from cadaveric donors.

No association is seen between food allergy and breastfeeding, number of siblings, age at introduction of solid food, occurrence of acute rejection or Epstein–Barr virus viraemia within the first year after liver transplantation. There was no difference in indication for liver transplantation (biliary atresia versus other indications) or number of patients who received intestinal surgery prior to transplantation between food-allergic and non-food-allergic patients.

Liver versus renal transplant recipients

Compared to the renal transplant group, median age at transplantation is significantly lower in the liver transplant group ($p<0.001$). The two groups do not differ in use of primary immunosuppression (tacrolimus versus cyclosporine) or basiliximab. However, significantly more renal transplant patients receive mycophenolate mofetil in association with calcineurin inhibitors ($p=0.28$).

Total eosinophil count is significantly higher in liver (270/ μ L (90–1,820)) versus renal (140/ μ L (0–340)) transplant

patients ($p<0.001$). Total IgE is also higher in liver transplant patients (24.4 kU/L (0–9930) versus 7 kU/L (0–157)) but does not reach statistical significance ($p=0.08$).

Age at introduction of solid food is comparable between renal and liver transplant patients. No significant difference is found when comparing the number of patients exposed to solids prior to transplantation.

Discussion

This study confirms that children after liver transplantation carry a high risk for the development of new onset food allergy. Thirteen out of 49 liver transplant patients developed food allergy compared to a general incidence of less than 5 % in young children in westernised countries [16].

Although our patient population is relatively small, the strength of this study lies in the monocentric follow-up of both renal and liver transplant patients by a small group of nephrologists and gastroenterologists working in close collaboration. Similar immunosuppression protocols are used in both groups allowing good comparison between the groups. Continuous follow-up by a constant team of physicians enabled extensive and detailed collection of clinical data.

Six out of 13 food-allergic patients exhibit acute onset, IgE-mediated, potentially life-threatening [9] signs such as angioedema, anaphylaxis. Two of 13 patients have non-IgE-mediated food allergy, demonstrating that IgE antibodies seem to be involved in the immunopathology in the majority of these patients [16].

Food allergies are often multiple and the majority of patients do not outgrow their symptoms. In the general population, the natural history of food allergy depends on the type of allergen, the involvement of IgE and the age of onset of food allergy. Most children with food allergy eventually will tolerate milk, egg, soy and wheat whilst far fewer will eventually tolerate tree nuts and peanut. A high initial level of sIgE against a food is associated with a lower rate of resolution of clinical allergy over time. Food allergy that starts later in life or in adults tends to persist [14]. Our patients, being initially tolerant to the food allergens, lost tolerance after liver transplantation. The natural course in this group might therefore be different from food-allergic children who primarily fail to achieve tolerance. The liver-transplanted children might hence have a course more similar to patients who develop food allergy later on in childhood and adult life, with a higher tendency to suffer from long lived food allergy.

Of note is that there was no difference in pre-transplant or post-transplant introduction of solid foods between food-allergic and non-food-allergic liver transplant patients and renal transplant patients. In all groups, food reintroduction after transplantation was not guided but at random, according

to patient's choice and age. Based on the data presented in this paper, however, a more careful gradual food introduction with a hypoallergenic feeding protocol might be indicated in patients particularly at risk for the development of food allergy (young children, viral gastroenteritis...).

Gastrointestinal complaints and mainly diarrhoea are frequent after liver transplantation. The underlying cause of post-transplant diarrhoea often remains unidentified. Commonly reported causes are infections (CMV, adenovirus, clostridium difficile, bacterial overgrowth, microsporidia, cryptosporidia, parasites...) and medication (mycophenolate mofetil, sirolimus, magnesium supplements, antibiotics...) [8]. Ten in 13 food-allergic patients presented gastrointestinal complaints (mainly diarrhoea), often appearing in the aftermath of an episode of viral gastroenteritis in the early post-transplant phase. The diagnosis of food allergy should therefore always be taken into account when confronted with persistent or unexplained gastrointestinal manifestations in children after transplantation. The combination of intestinal injury by viral infection and increased permeability caused by tacrolimus [7] therapy might impair the intestinal barrier against antigen uptake, favouring the vulnerability of these patients for the development of food allergy.

Three food-allergic children suffer from persisting, severe, treatment resistant cheilitis in association with oral mucosal lesions. Saalman et al. [15] reported long-standing oral mucosal lesions in solid organ-transplanted children as a novel clinical entity. Notably, most of these patients also had a clinical history of immediate-onset food-induced allergic reactions. Dietary elimination of food antigens causing these reactions, however, did not seem to improve the oral lesions. The same holds true in our patients: although elimination diet led to a resolution of other signs, the oral lesions and cheilitis persist. On the other hand, these lesions only are seen in patients with a history of food allergy. Saalman states that the coexistence of oral lesions and immediate onset allergic reactions may indicate that the oral lesions arise as a consequence of a dysregulated immune system and that other antigens, such as autoantigens or antigens of commensal microbes may be involved.

The immunosuppressive therapy in solid organ transplantation targets mainly the T and B cell-mediated immune response. Although there seems to be an insufficient control of allergen-specific responses via the regulatory T cell compartment under systemic immunosuppression [3].

When comparing food- and non-food-allergic liver transplant children, the use of tacrolimus as primary maintenance immunosuppression is associated with the occurrence of food allergy. Blood eosinophilia and increased serum IgE levels have been reported during tacrolimus treatment after liver transplantation. By inhibiting interleukin-2 and

regulatory T cells, tacrolimus causes a skewing towards a T-helper 2 immune response. Furthermore, tacrolimus has been shown to increase intestinal permeability [7]. In liver-transplanted adults, however, the widespread use of tacrolimus does not seem to be associated with an increase in food allergy. Also, despite similar use of calcineurin inhibitors, none of our paediatric renal transplant patients developed food allergy after transplant. Hence, we hypothesise that the use of tacrolimus, although likely an important predisposing factor, is definitely not the sole player in the development of post-transplant food allergy.

Age at time of transplantation seems to be an important risk factor as only children undergoing liver transplantation below the age of 3 years developed food allergy. Paediatric renal transplant recipients were significantly older at time of transplantation and did not develop food allergy. Immaturity of the immune regulatory mechanisms and gastrointestinal tract may contribute to the development of food allergy.

Interestingly, mean donor age is significantly lower in the food-allergic group compared to non-food-allergic liver transplant patients. More than half (7/13) of the food-allergic patients received a graft from very young (<6 year) paediatric donors compared to only 2 of 35 non-food-allergic patients. This finding, which has not been reported to date, is very intriguing and further supports the presumed critical role of the liver in tolerance development to food antigens and autoantigens. In a mouse model, the liver was found to be one of the sites at which T-helper 2 lymphocytes specific to a food antigen develop [18].

Immune dysregulation might already exist in chronic liver disease patients prior to transplantation. Liver transplantation together with the use of tacrolimus within a critical window of age (most often in combination with a young donor organ) seems to disturb immune tolerance against food proteins. Disruption of mucosal integrity (viral infections, tacrolimus use...) and alterations in gastrointestinal commensal flora (viral gastroenteritis, use of antibiotic, presence of Roux-en-Y loop...) might lead to both local (gastro-intestinal and oral mucosal) and systemic inflammatory reactions in which food antigens but potentially also autoantigens and/or antigens against commensal bacteria play a role. Previously, it has been shown that neonatal intestinal surgery on itself can increase the risk of food allergy [4, 5]. Extrahepatic biliary atresia is the major indication for paediatric liver transplantation. Furthermore, the majority of children transplanted at a young age undergoes split liver transplantation requiring hepaticojejunostomy. Early intestinal surgery, such as Kasai portoenterostomy and creation of the Roux-en-Y loop at time of transplant, in association with the use of postoperative antibiotics influence intestinal permeability, intestinal microflora and immune system and can hence increase the risk of postoperative food allergy.

Liver transplantation put patients at high risk for the development of food allergy having a major impact on their quality of life. Based on a detailed analysis of clinical data in paediatric liver and renal transplant patients, we conclude that the occurrence of post-transplant food allergy is associated with liver transplantation, tacrolimus use, young age at time of transplant and young donor age. The majority of our food-allergic patients was transplanted very early on in life, within a critical window of tolerance development, making them particularly vulnerable for the development of food allergy. Patients present multiple, persistent food allergies mainly with gastrointestinal signs. Chronic oral lesions resistant to dietary intervention are seen in 3 out of 13 food-allergic patients. IgE seems implicated in the immunopathology of post-transplant food allergy in the majority of patients.

Future prospective studies comparing the occurrence of food allergy in age-matched paediatric solid organ recipients are indicated to further identify precise risk factors. The potential benefit of a hypoallergenic feeding protocol in the immediate post-transplant period (when patients are maximally exposed to high doses of immunosuppression) or during episodes of viral gastroenteritis needs to be investigated in high-risk patients. Future research (both clinical and in vitro) should also focus on the effect of immunosuppression on the immature immune system and the development of immune tolerance. Based on these results, we might need to tailor the way we introduce foods after liver transplantation according to the age and risk profile of the patient and need to re-evaluate the immunosuppressive regimens currently used in very young transplant recipients.

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