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LIVER TRANSPLANTATION AND ALLERGY: TRANSPLANT-ACQUIRED FOOD ALLERGY

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SUMMARY

Transplant-acquired food allergy is a well known phenomenon especially linked to liver transplants. Risk factors lie both in transplant recipient and transplant donor - age of recipient and the maturity of immune regulatory mechanisms, family history of atopy in recipient, young age of the donor and atopic history in donor. The exact mechanism has not yet been established and there are many different explanations of this pathophysiologic process. Transplanted liver is a large and well perfused organ, rich in pluripotent hematopoietic stem cells and donor's IgE antibodies that can alter immunological response in the host. Some studies suggest that post-transplant immunosuppression with tacrolimus is linked to an increased occurrence of IgE-mediated sensitization and manifestation of allergic disease.

Research in the field of transplant-acquired food allergy is not important only for transplant patients and physicians involved but also for understanding the mechanism of food allergy development in general population and potentially reducing this global health concerning issue.

Key words: *food allergy – transplantation - transplant-acquired food allergy*

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INTRODUCTION

Organ transplantation is a life-saving procedure performed in a variety of clinical settings - end-stage organ failure, cancer, and autoimmune disorders. Transplantation medicine is a rapidly growing field that has made procedures relatively safe and efficient with rare adverse reactions. One of the very rare adverse reaction is a transplant-acquired food allergy (TAFA) after bone-marrow or solid organ transplantation.

This phenomenon is already well known in scientific literature and many cases and reviews are published since 1980s. The most common patients are children, especially after liver transplantation.

The direct cause of this adverse reaction is not well established, but there are many different mechanisms that could potentially lead to recipient's sensibilization. Recognizing and understanding these mechanisms, apart from explaining the phenomenon of 'transplant-acquired food allergy', can greatly help in cognition of nutritive antigens tolerance-loss in un-transplanted population with 'food-allergy', a condition that presents a growing medical concern.

Therapeutic modalities are still very limited, but awareness of this phenomenon, diagnostic possibilities and early recognition of potentially life-threatening condition represent an important subject in the fast growing field of transplantation medicine.

The aim of this review is to elucidate the phenomenon of transplant-acquired food allergy, it's clinical presentation, risk factors and underlying mechanisms.

FOOD ALLERGY: DEFINITION, MECHANISMS AND RISK FACTORS

Food allergy is an immunologically mediated adverse response to nutritive antigens. The most common nutriative allergens are milk, egg, peanut, tree nuts, shellfish, fish, wheat, sesame and soy. Food allergy is usually presented in childhood and the most cases cease with adulthood. The patient presents a wide variety of symptoms in contact with incriminated food, from mild skin changes, through gastrointestinal and respiratory problems and all the way to life-threatening anaphylaxis that requires fast and accurate recognition and urgent therapy. This type of disease significantly influences the quality of life both the patients' and their families and, apart from the health issue, presents also a sociological and economic burden.

Food sensibilization is a complex interaction of both environmental and genetic components. Food allergy develops through several steps - development of oral tolerance, sensitization to food allergens and anaphylactic reactivity to allergens. Oral tolerance is a physiological concept that enables food intake without activating immune response to ingested antigens. It is regulated by specific gut-resident cells and T regulatory cells that are able to maintain a tolerant environment toward food antigens. This fine balance can be violated by relatively unclear pathophysiological cascade that includes changes in the microbiome, cytokine imbalances and loss of epithelial barrier integrity. These changes lead to gut sensitization and clinical presentation of food

allergy immediately, or with several hours delay after allergen ingestion. A symptoms are the result of antibodies immunoglobulin E (IgE) and IgG action, the release of pre-formed mediators such as histamine by mast cells and basophils, and the recruitment and build up of inflammatory cells.

Epidemiological studies of food allergy prevalence define some risk factors like sex (male children, female adults), race (Asian and African-American children) other atopic disorders, diet (deficiencies of either vitamin D, antioxidants, or omega-3-polyunsaturated fats), obesity, use of antacids, hygiene, and maternal diet (Sicherer & Sampson 2014). Especially strong risk poses family history of food allergy and mutations in specific genes. There is a significant link between mutations in the *filaggrin* gene, which codes for an epidermal protein critical to skin barrier function, and food allergy in children (Venkataraman et al. 2014).

FOOD ALLERGY AFTER ORGAN TRANSPLANTATION: RISK FACTORS

Acquiring food allergy after organ transplantation is well-known phenomenon. It occures to a variety of allergens, including nut, milk, egg, wheat, and fish. Onset-time varies from days to months after transplantation. It is described after different types of transplants - bone marrow, liver, kidney, heart, intestine and lung, in both adult and pediatric patients. Epidemiology data show rather high prevalence of transplant-acquired food allergy in children stated as 17%, majority after orthotopic liver transplantation. There are some reports on the resolution of food allergy over time, probably due to reduced immunosuppression and avoidance of nutritive allergens (Mavroudi 2012). Throughout history of scientific literature there are many reports on this phenomenon - the earliest reported cases of transplant-acquired food allergy involved bone marrow transplantations in two non-allergic children that developed nutritive allergies; the donors were siblings who had a history of atopy (Tucker & Barnetson 1985, Walker et al. 1986) First published cases after solid organ transplantation appeared almost a decade latter (Legendre et al. 1997, Lacaille et al. 1997) and reporting on additional cases continued to date. Given studies show that risk factors for this adverse event lie both in transplant recipient and transplant donor, therefore it seems hard to determine the key factors. Many reports have shown that transplant-acquired food allergies are more common after liver transplantation, especially in pediatric population. It can easily be observed that there must be something unique about immunology of the liver that is causing this condition. Here are some proposed mechanisms for this phenomenon. Firstly, the liver contains pluripotent hematopoietic stem cells which are able of generating lymphocytes in donor's body after transplantation and these lymphocytes may be sensitized to a particular allergen and potentially produce an immune response in the recipient upon allergen exposure. Secondly, liver is a rather large, well perfused organ so the transfer of pluripotent hematopoietic stem cells is more likely than with smaller organs and lesser cell count (Trotter et al. 1997). Also, transfer of resident dendritic cells and sinusoidal endothelial cells to the recipient can alter naive CD4+ T cells toward a Th2 phenotype, promoting an IgE response to antigen (Watanabe et al. 2003). There is, as well, an interesting theory of children with food allergy prior to transplantation, but with immune dysfunction due to liver failure and inability to produce clinical features; these patients demonstrate allergy signs just after recovering liver function after transplantation (Boyle et al. 20015). Age of recipient is second important factor of developing transplant-acquired food allergies. Data show significantly higher prevalence of condition in children. This is in accordance with general prevalence of food allergy in population (Sicherer & Sampson 2014.). Recipient's family history of atopy is not a negligible risk factor - it is shown that that even 50% of liver recipients that developed food allergy had a family history of atopic disorders (Lykavieris et al. 2003).

Donor specific factors certainly include atopic history but this may not be the sole factor involved. According to some reports, young age of the donor can also be significant predisposing factor (Ozdemir 2013).

FOOD ALLERGY AFTER ORGAN TRANSPLANTATION: MECHANISM

The exact mechanism has not yet been established and there are many different explanations of this pathophysiologic process. Certainly, there is no sole mechanism responsible, rather combination of multiple factors, both in donor and in organ immunology. The most mentioned mechanism is the passive transfer of donor allergen-specific IgE antibodies during the transplantation procedure. IgE antibodies are bound to mast cells and can survive long enough to cause degranulation after exposure to the particular food allergen.

Another frequently pointed mechanism is the transfer of allergen-specific B or T lymphocytes within the donated organ. Liver, as a important source of hematopoietic stem cells, is able to produce allergen-specific lymphocytes. These lymphocytes can persist for months in the recipient (Needham 2015).

As an incriminated factor, in literature is frequently mentioned immuno-supressant drug *tacrolimus.* Tacrolimus affects intestinal barrier function and changes its permeability (Gabe et al. 1998). Consequently, nutritive allergens penetrate the intestinal barrier, facilitating susceptibility to food allergens. *Tacrolimus* also disrupts the Th1/Th2 balance towards IL-4, IL-5, and IL-13, the main mediators of allergies (De Bruyne et al. 2013). A study by Gruber et al. directly compared the occurrence

of allergic sensitization and disease under *tacrolimus*-versus *cyclosporine A*-based immunosuppressive therapy in kidney-transplanted patients. The rate of clinically relevant allergy in patients receiving *tacrolimus* was twice that in patients receiving *CsA* (15% *vs.* 8%), (Gruber et al. 2011).

CONCLUSIONS

Transplant-acquired food allergy presents a very intriguing subject in the wide field of transplantation medicine and adds one more possible risk on the long list of post-transplantation adverse events. Transplant physicians, as well as organ recipients, should be aware of this phenomenon, clinical presentation and, if necessary, immediate adrenaline therapy. Prior to the procedure, allergic status and family history of atopy in recipient and in donor should be documented.

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Jadranka Pavičić Šarić & Jelena Zenko: study design, data collection, first draft, approval of the final version.

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