

Acquired atopic disease after liver transplantation in children; similarities to and differences from adults: a preliminary study

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Objective The aim of this study was to determine the similarities and differences in the frequency and follow-ups of newly diagnosed atopic diseases after liver transplantation in pediatric and adult patients.

Materials and methods Patients who underwent liver transplants between 2005 and 2013 and who are still alive were enrolled in the study. Patients who came for checkups filled out a survey evaluating atopic diseases. Those who had an atopic disease before transplantation were excluded from the study.

Results A total of 165 patients were enrolled in this study; 114 (69.1%) were males and 29 (17.6%) were children. The average transplantation age was 40.8 (0.3–67) years, and the most frequent reason for transplantation was chronic viral hepatitis. In 22 patients, atopic diseases [allergic rhinitis in nine patients (5.5%), asthma in six patients (3.9%), atopic eczema in six patients (3.9%), food allergy in six patients (3.9%), and drug allergy in one patient (0.6%)] developed after transplantation. Atopic diseases after transplantation were more common in children ($P = 0.03$). When the atopic diseases were examined on a case-by-case basis, there were no differences between children and adults with respect to asthma ($P = 0.284$), allergic rhinitis

($P = 1.0$), or atopic eczema ($P = 0.284$), but food allergy ($P = 0.009$) and peripheral eosinophilia ($P = 0.002$) were more common in children. The periodicity of allergic diseases after transplantation ($P = 0.192$) and total IgE levels ($P = 0.086$) were similar.

Conclusion Atopic diseases developed after liver transplantation and had a greater impact on children than adults. Therefore, after undergoing liver transplantation, patients should be monitored closely for signs of atopic diseases. *Eur J Gastroenterol Hepatol* 26:1055–1059
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European Journal of Gastroenterology & Hepatology 2014, 26:1055–1059

Keywords: atopic disease, children, liver, transplantation

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Received 30 March 2014 Accepted 14 May 2014

Introduction

In recent years, the number of studies on newly diagnosed atopic diseases after solid organ transplantation has been increasing [1–3]. Post-transplantation atopic diseases might present with anaphylaxis, which is a life-threatening allergic reaction, or asthma or eczema, which impair quality of life [2–4]. The most common atopic diseases are food allergies, with a frequency rate of 5.6–37% [1,3]. The pathogenesis of allergic diseases (especially food allergies) that develop after solid organ transplantation is still not clearly understood. However, it is believed that tacrolimus, an immunosuppressive agent used to prevent the rejection of tissue, might contribute toward the development of atopic diseases. Tacrolimus affects the barrier function of the intestines and alters their permeability [5,6]. As a result, food allergens pass through the intestinal barrier and facilitate the development of greater sensitivity against food allergens. Furthermore, tacrolimus disturbs the balance between Th1 and Th2 which leads to an increase in the production of interleukin-4 (IL-4), IL-5, and IL-13. These cytokines are the main mediators of atopic disease [7].

However, tacrolimus use alone is not enough to account for the development of atopic diseases. Given that the transplanted solid organ was the liver and that the transplantation group included children, the study showed an increase in the development of atopic diseases.

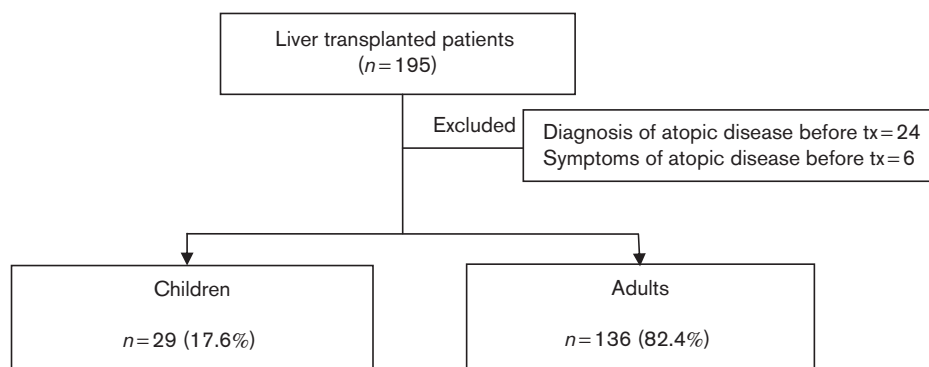
In the studies carried out to date, although both children and adults who underwent liver transplantation have been examined, none of the studies investigated the similarities and differences with respect to atopic diseases. In this study, the similarities and differences in demographics, atopic diseases (asthma, allergic rhinitis, atopic eczema, and food allergy), peripheral eosinophilia, and total IgE levels were examined in both pediatric and adult patients.

Materials and methods

Study population

Patients who underwent liver transplantation at the Inonu University Medical Faculty Transplantation Clinic between 2005 and 2013 were enrolled in this study. During their regular visits, patients and their donors (if

Fig. 1



Study flow chart. tx, transplantation.

they could be reached) were asked to fill out a survey prepared by an allergist to evaluate allergic diseases. This survey form included demographic information of the patient, cause of liver failure, duration of failure before transplantation, age at which the transplantation was performed, from whom the liver was obtained, affinity degree, atopic disease history of the donor, immunosuppressant treatments, symptoms of allergic diseases that developed after transplantation, and how soon the symptoms appeared after transplantation. The survey was used to evaluate the patients before and after transplantation. Patients who had symptoms of atopic diseases or who were diagnosed with atopic diseases before transplantation were excluded from the study (Fig. 1).

Characterizations

Patients who presented atopic disease symptoms were examined in the allergy clinic to confirm the diagnosis. Serum total IgE levels, peripheral eosinophil counts, skin-prick test for allergic sensitivity, and/or serum-specific IgE levels were determined. Respiratory function tests were performed on patients who presented asthmatic symptoms; skin tests were performed on patients who presented food or drug allergies; and oral provocation tests were performed with food and drugs on patients who were still suspected of having a food or a drug allergy despite negative skin tests. *Asthma diagnosis* was made according to the Global Initiative for Asthma (GINA) guidelines [8], *allergic rhinitis diagnosis* was made according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline [9], and *atopic eczema diagnosis* was made according to the Hanifin and Rajka [10] criteria on the basis of patient history and clinical characteristics.

Immediate-type reactions such as urticaria, angioedema, and anaphylaxis and delayed-type reactions such as colitis and atopic eczema exacerbation were defined as food allergies. In patients who presented an immediate or a delayed reaction after taking drugs, positive skin tests (if the allergen was available) or positive oral drug

provocation tests were defined as drug allergies. Skin-prick tests were performed using prick reagents (Alyostal; Stallergenes, Antony, France) and prick-to-prick tests were performed with fresh food. Histamine and sodium chloride (0.9%) were used as positive and negative controls, respectively. Specific IgE was measured using the ImmunoCAP assay for foods. A level of at least 4% of peripheral eosinophils was defined as eosinophilia.

The patients who were enrolled in the study provided informed consent, and the study was approved by the Ethics Committee of Inonu University (approval number 139/10.09.2013).

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, Illinois, USA). A descriptive analysis was used to characterize the patients. Qualitative variables are expressed as frequency and percentage and quantitative variables are expressed as medians. Comparisons between groups were made using Pearson's χ^2 -test (Fisher's exact test when needed) and the Mann-Whitney *U*-test. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Demographics

A total of 165 patients were enrolled in the study; 114 of the patients (69.1%) were males and 29 (17.6%) were in the pediatric group. The median transplantation age was 40.8 (0.3–67) years and the most frequent reason for transplantation was end-stage liver disease because of chronic viral hepatitis. Twenty-one of the patients (12.7%) had undergone cadaveric liver transplantation and the remaining patients had undergone living-related liver transplantation. The median period of liver failure before transplantation was 6 (1–120) months and the median follow-up period after transplantation was 14 (1–100) months (Table 1). For immunosuppression after

Table 1 Demographics of patients who underwent liver transplantation (*n* = 165)

Variables	Children (<i>n</i> = 29) [<i>n</i> (%)]	Adults (<i>n</i> = 136) [<i>n</i> (%)]	<i>P</i> value
Male	14 (48.3)	100 (73.5)	0.014^c
Median duration of liver failure (min–max) (years)	5 (0–120)	6 (0–60)	0.154
Median age at the time of transplantation (min–max) (years)	5.1 (0.3–16.1)	44.6 (17.3–67.4)	<0.001^d
Median duration of follow-up (min–max) (months)	14 (1–47)	13 (1–100)	0.267
Type of transplantation			
Cadaveric organ	6 (20.7)	15 (11)	0.267
Living related	18 (62.1)	110 (80.9)	0.500
Living nonrelated	5 (17.2)	11 (8.1)	0.162
Indication of liver transplantation			
Cholestatic liver disease	5 (17.2)	2 (1.5)	0.002^c
Viral infection, chronic	8 (27.6)	99 (72.8)	<0.001^c
Fulminant (viral, drug, toxic)	7 (24.1)	5 (3.7)	0.001^c
Metabolic ^a	5 (17.2)	9 (6.6)	0.074
Idiopathic	4 (13.8)	16 (11.8)	0.757
Other ^b	–	5 (3.7)	–
Chronic immunosuppressant regimen			
Tacrolimus	20 (69)	75 (55.1)	0.246
Cyclosporin	3 (10.3)	4 (2.9)	0.198
Tacrolimus and mycophenolate mofetil	3 (10.3)	45 (33.1)	0.260
Tacrolimus and everolimus	3 (10.3)	12 (8.8)	0.729

Numbers in bold indicate statistical significance.

^aWilson's disease = 13, α -1 antitrypsin deficiency = 1.

^bHepatocellular carcinoma = 2, Budd–Chiari syndrome = 2, alcoholic liver disease = 1.

^cChi-square test.

^dMann–Whitney U-test.

liver transplantation, 95 patients (57.6%) were treated with tacrolimus, seven patients (4.2%) were treated with cyclosporine, 48 patients (29.1%) were treated with tacrolimus and mycophenolate mofetil, and 15 patients (9.1%) were treated with immunosuppressants that included tacrolimus and everolimus. Atopic diseases developed in 22 patients (13.3%) after transplantation [allergic rhinitis, asthma, atopic eczema, food allergy, and drug allergy in nine (5.5%), six (3.9%), six (3.9%), six (3.9%), and one (0.6%) patients, respectively]. Food allergies against eggs, bananas, and lentils developed in four, one, and one patients, respectively. Urticaria developed in five patients and anaphylaxis developed in one patient. Eosinophilia was present in 28 patients (17%).

Similarities and differences between children and adults Demographics

When the indication for liver transplantation was examined, it was observed that acute fulminant liver failure and cholestatic liver disease were more common in children ($P=0.001$), and that chronic liver failure because of chronic viral hepatitis was more common in adults ($P<0.001$). In the adult group, liver transplantation was performed more often in male patients ($P=0.014$). Duration of liver failure before transplantation, follow-up duration after transplantation, use of a living donor, and immunosuppressant agents administered were all similar between the adult and the pediatric groups (Table 1).

Acquired atopic disease after liver transplantation

The development of atopic diseases after liver transplantation was more common in children than in adults (27.6 vs. 10.3%; $P=0.03$). When atopic diseases were examined on a case-by-case basis, there were no differences between children and adults with respect to asthma ($P=0.284$), allergic rhinitis ($P=1.0$), or atopic eczema ($P=0.284$), but food allergy ($P=0.009$) and peripheral eosinophilia ($P=0.002$) were more common in children. The periodicity of allergic diseases after the liver transplantation ($P=0.192$) and the total IgE levels ($P=0.086$) were similar (Table 2).

Discussion

In our study, 13.3% of the patients developed atopic diseases after liver transplantation. When the children were compared with the adults, it was observed that the development of asthma, allergic rhinitis, and eczema was similar, but food allergy and peripheral eosinophilia were more common in the children.

When liver transplantation indications were examined, fulminant and cholestatic causes were the most common in children, and chronic viral hepatitis was the most common indication in adults. Similarly, Noble *et al.* [2] reported that in 78 children, the most common indication of liver transplantation was cholestasis. Agopian *et al.* [11] reported that in adult patients, the most common indication of liver transplantation was chronic viral hepatitis.

In recent years, medical studies have reported that atopic diseases develop after solid organ transplantation [1–3]. In particular, food allergies have been shown to develop after liver transplantation rather than other solid organ transplantations, such as the kidney [12]. The most commonly developed atopic disease is food allergy, and it particularly affects young children who have a transplanted liver. In the study carried out by Shroff *et al.* [3], of the 176 children evaluated with respect to atopic disease after transplantation, 25 (14.2%) developed an atopic disease. However, Noble *et al.* [2] reported that 78% of the children enrolled in their study developed an atopic disease. In our study, 13.3% of the patients developed atopic diseases. These differences among studies can be attributed to differences in the methods used. Shroff *et al.* [3] did not include drug allergies in their study, whereas Noble *et al.* [2] included allergic reactions resulting from drugs and diseases such as eosinophilic esophagitis in their study. The methodology of our study differed from those of the other studies in that it included atopic diseases such as asthma, allergic rhinitis, eczema, and food and drug allergies. Furthermore, in contrast to the other studies, atopic disease was not diagnosed through family definition and survey questioning, but rather, atopic disease symptoms were evaluated in all of the patients by allergists, and those with a confirmed allergy diagnosis were included in the study.

Table 2 Comparison of children and adults with acquired atopic disease after liver transplantation

	Children (n = 29) [n (%)]	Adults (n = 136) [n (%)]	P value ^c
Atopic disease	8 (27.6)	14 (10.3)	0.03
Asthma	2 (6.9)	4 (2.9)	0.284
Allergic rhinitis	1 (3.4)	8 (5.9)	1.0
Atopic eczema	2 (6.9)	4 (2.9)	0.284
Food allergy	4 (13.8)	2 (1.5)	0.009
Drug allergy ^a	—	1 (0.7)	—
Atopic disease in donor ^b (n = 144)	—	5 (4.1)	—
Median time to first symptoms of allergy after tx (months)	7 (2–13)	12 (1–36)	0.192
Median total IgE level, post-transplant (n = 122)	24.9 (4.5–539)	43.2 (2.5–2000)	0.086
Peripheral eosinophilia, post-transplant (n = 165)	11 (37.9)	17 (12.5)	0.002

Numbers in bold indicate statistical significance.

^aNaproxen sodium.

^bAsthma, allergic rhinitis, atopic eczema, food allergy, drug allergy.

^cChi-square test.

Food allergies have mainly been studied with respect to atopic diseases that developed after liver transplantation [12–14]. Some studies have reported that the development of food allergies after transplantation was observed in 37.6% of children [1]. Eggs and milk are the main foods responsible for causing allergies [3,13]. In our study, one-quarter of the atopic diseases were food allergies, the most common of which was egg allergy.

It is believed that tacrolimus contributes toward the development of atopic diseases after organ transplantation. Because tacrolimus has an immunosuppressant effect by preventing the production of IL-2 on Th1 cells, it leads to a shift in balance between Th1 and Th2 to Th2. A shift to a Th2 CD4⁺ immune response has been proposed as a cause of allergic diathesis [7]. However, in the development of atopic diseases in all patients who took tacrolimus, fewer cases of food allergies have been observed in solid organ transplantations other than the liver, thus suggesting that tacrolimus alone is not enough to account for the development of food allergies.

In the limited studies carried out on atopic diseases after liver transplantation, it has been shown that food allergies and other atopic diseases occur more commonly in children. Unlike previous studies, we compared the similarities and differences between children and adults in terms of atopic diseases that developed after transplantation. The atopic diseases that developed in children were similar to those of adults, with the exception of food allergies, which, along with peripheral eosinophilia, were more common in children. The reason for this difference is considered to be that the effect of tacrolimus is more prominent in younger ages. The study by Gabe *et al.* [6] showed that tacrolimus inhibited the production of energy in intestinal mucosa epithelium cells and increased the permeability of cells. It is possible that the increase in intestinal permeability favors the transport of antigens from the intestinal lumen, in turn increasing the risk of sensitization and the development of food allergies. The substantial effect of tacrolimus on children and the rapid growth of cells partially explain why food allergies are more common in this age group.

One of the limitations of our study was its retrospective nature, which prevented the measurement of total IgE, peripheral eosinophils, and sensitivity of allergens before transplantation. Another limitation is that the donors were not examined in terms of passive allergen transfer.

Conclusion

Atopic diseases develop after liver transplantation, and food allergies in particular develop more frequently in children than in adults. Therefore, patients should be monitored closely with respect to atopic diseases after liver transplantation and patients should be asked about any atopic disease symptoms in the follow-up.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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