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Invited Review

Childhood Organ Transplantation

Çocukluk Çağı Organ Transplantasyonları

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ABSTRACT

Organ transplantation has significantly changed the life expectancy of patients with advanced organ failure. The quality of life with transplanted organs and their impact on growth have become more critical for children as they have a much longer life expectancy and will be experiencing growth stages. Solid organ transplantation techniques, which were used only experimentally in animals until the middle of the 20th century, have become a treatment option in the 21st century. Particularly with the discovery of new immunosuppressive drugs in the 1960s, transplantation has gained impetus as a viable therapeutic option. Examination of the biopsies taken from the transplanted organ is an important factor that ensures early recognition of rejection findings and can prolong the life of the organ. In this review, the historical development of transplantation, the mechanisms involved in tissue rejection, rejection evaluation criteria, and the main differences between childhood and adult organ transplantations are briefly reviewed.

Keywords: Solid organ transplantations, transplantation pathology, rejection criteria, childhood, and adulthood transplantations

ÖZ

Organ nakli, ilerlemiş organ yetmezliği olan hastaların yaşam beklentisini önemli ölçüde değiştirmiştir. Nakledilen organlarla sürdürülen yaşamın kalitesi ve nakil sonrası kullanılan ilaçların büyüme üzerine etkisi, çok daha uzun bir yaşam beklenen ve büyüme evresinde olan çocuklar için daha kritik hale gelmiştir. Yirminci yüzyılın ortalarına kadar sadece hayvanlarda deneysel olarak kullanılan solid organ nakli teknikleri, 21. yüzyılda bir tedavi seçeneği haline gelmiştir. Özellikle 1960'lı yıllarda immün sistemi baskılayan yeni ilaçların bulunmasıyla birlikte transplantasyon önemli bir ivme kazanmıştır. Transplante organdan alınan biyopsilerin incelenmesi ret bulgularının erken fark edilmesini sağlayıp, organın ömrünü uzatabilen önemli bir unsurdur. Bu derlemede transplantasyonun tarihsel gelişimi, doku reddinde rol oynayan mekanizmalar, rejeksiyon değerlendirme kriterleri ile çocukluk çağı ve erişkin organ transplantasyonları arasındaki temel farklar kısaca gözden geçirilmiştir.

Anahtar kelimeler: Solid organ transplantasyonları, transplantasyon patolojisi, rejeksiyon kriterleri, çocukluk çağı ve erişkin dönem transplantasyonları

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INTRODUCTION

Although dreams of transplantation go back to the 3rd century AD, this vision only came true at the end of the 20th century[1]. The first successful human organ transplantation was kidney transplantation from a twin performed by Joseph Murray in the year 1954 which allowed the recipient to live for 8 more years[1,2]. With the discovery of immunosuppressive drugs, organ transplantation has gained momentum since the 1960s[2-4]. Pediatric organ transplantation has greatly improved the management and survival of treatment-resistant pathological conditions in children with end-stage organ failure and is now considered the treatment of choice when clinically appropriate. In the pediatric age group, various organs and tissues including the heart, kidney, liver, lung, intestines, pancreas and bone marrow can be transplanted[5-7].

When compared with relevant official records on transplantation, in the USA, which has the largest patient series in solid organ transplantation, approximately 20 thousand renal transplantations, almost all of them from deceased donors, and about 7,000 liver transplantations, of which about 1/4 of them from living donors, were performed in 2017[4].

In childhood, organ transplantation can represent as a challenging and complex treatment option, especially due to the extent of surgical intervention, immune system response, use of immunosuppressive drugs, and the unfavorable effects of all these processes on growth,

skeletal development and quality of life. Advances in immunosuppressive therapies have significantly improved patient care and graft survival rates, but the long-term risks of these therapeutic interventions are not well known due to the lack of randomized clinical trials performed in the pediatric population[5-7].

The aim of this review is to examine the differences between organ transplantations performed in pediatric age and in adults after briefly summarizing the mechanisms that play a role in organ rejection and criteria of rejection.

MOLECULES THAT PLAY A ROLE IN ALLOGRAFT REACTIVITY

1) Major histocompatibility complex (MHC)

The MHC, which plays the most important role in tissue rejection, was identified by Jean Dausset in the 1950s and is termed as human leukocyte antigen (HLA)[1,2]. The MHC system encodes for two major protein groups in humans: Class I (HLA-A; B; C) and Class II (HLA-DP, DQ, DR). MHC class I transmembrane molecules are found in almost all nucleated cells, while MHC class II molecules are mainly found in B lymphocytes, macrophages and dendritic cells. However, some immunomodulatory molecules such as interferon gamma (IFN-γ) can increase MHC class II expression on many cell surfaces, especially endothelium, epithelial cells, and T lymphocytes. Normally, MHC class I molecules present antigenic peptides such as viral antigens and oncogenic products to T lymphocytes. MHC class I molecules and the antigenic peptide complex are recognized by specific cytotoxic CD8 (+) T lymphocytes. T cells are stimulated and these infected cells or those altered by an oncogenic effect are destroyed. On the other hand, MHC class II cells present exogenous antigenic peptides in the extracellular pool to CD4 (+) helper T lymphocytes. However cross presentations are also possible. MHC molecules are highly polymorphic, which provides a high level of immunity against pathogens that constantly mutate[8,9].

2) Minor histocompatibility antigens (MiHAs)

MiHAs are small peptides that coexist with MHC class I or class II molecules on the cell surface. Because of their polymorphic structure and their expression on the hematopoietic cell surface, they are effective in the molecular presentation of self to the immune system. Even differences in a single amino acid can be detected by immunoreactive T cells and can cause graft-versus-host disease (GVHD) in HLA-matched allogeneic stem cell transplantation. While MHC antigens can be detected by both B and T lymphocytes, the response to MiHC antigens appears to be strictly T cell mediated. Although more than one hundred minor tissue compatibility antigens have been identified and sequenced, little data are available regarding the role of MiHA variations in the development of GVHD[10,11].

3) Tissue specific antigen (TSA)

As its name suggests, TSAs are antigens specific to different tissues or organs[1]. Central tolerance to TSAs is under tight thymic control, and autoimmune diseases develop when this control is disrupted. Although their role in transplantation immunobiology is still not fully elucidated, TSAs are known to enhance the host's immune response to the allograft. For example, myosin, which has not normally immunogenic characteristics, becomes immunogenic only when the transplant organ is injured, leading to an organ-specific response[1,2].

4) Donor specific antibody (DSA)

DSAs are recipient antibodies that can bind to MHC class I and II molecules in the transplanted organ, potentially causing graft injury. DSAs are formed by prior exposure to foreign antigens due to various blood product transfusions, previous pregnancies, autoimmune and viral diseases, and are present at the time of transplantation. However, *de novo* DSAs are formed after transplantation in response to genetically disparate HLA molecules of the new donor organ; young age is a risk factor for increased DSA formation. For the early detection of antibody-mediated rejection, regular measurement of DSAs in the blood is necessary. These antibodies often target endothelial cells thereby initiating a reaction with complement in the vascular wall, activating the coagulation cascade and releasing inflammatory mediators. The complement fragment, C4d, is formed during complement activation by the classical pathway. However, unlike other complement fragments, it does not disappear quickly and can be observed in the vessel wall for at least a few days. In most biopsies of transplanted organs or tissues, immunohistochemically detected C4d positivity on capillaries is accepted as additional evidence of an antibody-mediated rejection[1,2,12,13].

TISSUE REJECTION MECHANISMS

The reactions that occur because of different interactions of MHC, MiHA and TSA between recipient and donor are in the form of host-versus-graft (HVG) reactivity or GVHD. In HVG reactivity, the host immune

system recognizes these foreign MHC, MiHA, and TSAs antigens after organ transplantation. If this reaction cannot be prevented, the result is allograft rejection. Organ rejection is generally classified as hyperacute, acute, subclinical, and chronic. Hyperacute rejection develops within minutes or hours and is dependent on the presence of pre-existing antibodies. Acute and subclinical response is usually T cell and/or antibody-mediated rejection and develops within a few days or months. It can be reversible with immunosuppression. Chronic rejection develops months to years after transplantation and is typically unresponsive to treatment. In a sense, chronic rejection is closely related to the functional lifespan of the transplant organ. In the direct pathway, donor MHC molecules are presented to CD4 and CD8 T lymphocytes by donor-antigen presenting cells. The indirect mechanism develops more slowly and is effective in situations that predispose to chronic rejection. The third pathway is the semidirect pathway. In this pathway, recipient dendritic cells present donor MHC molecules to T lymphocytes. NK and NKT cells also play a role in organ rejection[1,14-16].

GVHD is a critical complication that is more common in organ transplantations involving massive hematopoietic cells such as hematological stem cell transplantation or multivisceral organ transplantation. GVHD can also develop acutely or chronically. The target organs of acute GVHD are mainly skin, liver, intestines, lung and lymphoid tissues. Inflammatory cytokines (e.g., tumor necrotizing factor alpha, interleukin 1), microbial lipopolysaccharides and necrotic cells that pass into the circulation from damaged organs are partly responsible for this stimulation. This activation facilitates the recognition of MHC and MiHA molecules by mature donor T cells and NK cells[1,14-16].

GRAFT INJURY MECHANISMS

1) Ischemia and innate immune activation: These complications are more frequently seen in transplantation from cadaveric donors. Increase of MHC and MiHA molecules and many molecular mechanisms such as Toll-like receptors and heat shock proteins play a role[1].

2) Acute rejection: It can develop as antibody - or T cell-mediated rejection.

a) In acute antibody-mediated rejection, anti-HLA antibodies or DSAs may develop in the recipient due to transfusions, pregnancy, or previous transplantation. These antibodies are typically IgM and IgG, with activation of many mechanisms. The presence of C4d and less commonly C3d are indicators of antigen-antibody interaction[1].

b) T cell-mediated rejection is the most common form of acute rejection observed in allografts. It is characterized by the collection of mononuclear cells, mainly lymphocytes and macrophages, in the connective tissue elements such as the interstitial areas. These inflammatory cells, led by T cells, attack mainly vascular structures and epithelial cells. The main targets are tubules in the kidney, bile tubules in the liver, and crypt epithelium in the gastrointestinal tract. Although T lymphocytes play the leading role, NK/NKT cells, monocytes/macrophages, plasmacytes, eosinophils and B lymphocytes also participate in this process. Since one of the important mechanisms working in T cell-mediated rejection involve some enzymes from the perforin/granzyme family used by CD8 (+) T lymphocytes and NK cells, their immunohistochemical detection in tissue or urine supports rejection diagnosis. In some studies, it has been reported that the presence of CXCR3 and CCR5 chemokines were evidence of rejection and their blockage is important in preventing T-cell mediated rejection[1,2,17].

3) Chronic rejection is also an important cause of recipient morbidity and mortality. Although acute rejection rates have been significantly reduced by immunosuppressive treatments developed in the last 20 years, the accumulation of fibroelastic material in various compartments of organs due to obliterative vascular injury, which is a chronic rejection symptom, is not prevented. The typical lesion is progressive arteriopathy involving small and large muscular arterial walls. It differs from atherosclerosis with its diffuse distribution, minimal lipid deposition, and lamination with adventitial scarring with intimal hyperplasia. All immunological processes between donor and recipient, from ischemia-reperfusion injury to acute and subclinical rejection episodes, affect chronic rejection. This process is regeneration and the fibroplasia phase that follows regeneration. Many chemokines aid in fibrosis. Although transforming growth factor-beta (TGF-β) is mainly responsible for this process, angiotensin II and plasminogen activator inhibitor are also involved[1,2].

4) Post-transplant infections are mainly caused by cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus (HHV-6, 7, 8) and hepatitis C virus (HCV)[1,2].

5) Recurrent and/or *de novo* immune disease are most evident in kidneys, and focal segmental

glomerulosclerosis (FSGS); immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, fibrillary GN, dense deposit disease, anti-glomerular basement membrane disease, and lupus nephritis are the most common diseases that develop in allografts[1,2].

6) Drug toxicity also causes very different clinical and histopathological changes[1,2].

TRANSPLANTATION PATHOLOGY

Today, there are different grading systems in transplantation pathology for each organ used. Banff classification is the most famous of these grading systems used in different organ transplantation pathologies, mainly in renal transplantations. Banff is a settlement located in the Canadian province of Alberta, and after the transplantation committee held its first meeting in Banff in 1991, Banff grading began to be used as the principal scoring system[18].

1) Evaluation of Kidney Biopsies

The latest Banff 2019 update is used for evaluation of kidney transplant biopsies. Zero-day biopsy sampling is often performed in order to make comparisons in subsequent evaluations. For ideal evaluation, at least 10 glomeruli and 2 arteries should be found in the biopsy material. The changes observed in the allograft are evaluated in 6 categories according to the Banff grading system as follows: normal; antibody-mediated rejection; borderline changes (suspect T-cell-mediated rejection); T-cell-mediated rejection; interstitial fibrosis/tubular atrophy, and other changes. In antibody-mediated rejection (humoral immunity) the capillaries around the kidney tubules are targeted. Glomeruli are also the main targets as they are made up of capillary tufts. Evidence of the presence of circulating alloantibodies is the circumferential deposition of C4d in the glomerular and peritubular capillaries. To be able to say antibody-mediated rejection, all three groups of changes such as the presence of tissue injury findings mainly affecting the capillaries (g, ptc or v>0), C4d positivity showing antibody association with the vascular endothelium, and the presence of DSA developed serologically against HLA or other antigens should be present in combination. Category 3, described as borderline changes in the Banff classification, is suspected acute T cell-mediated rejection. Intimal arteritis should not be found. Because in the presence of intimal arteritis, the diagnosis is cellular rejection. Minimal interstitial infiltration (i0 V i1) is accompanied by tubulitis (t1, t2, t3) or with minimal tubulitis (t1) in the infiltration phase (i2, i3). With T cell-mediated (cellular rejection) rejection, T lymphocytes target the tubules and the endothelium of the arteries. Its histopathological appearance is indistinguishable from tubulointerstitial nephritis[1,2,18-20].

2) Evaluation of Cardiac Biopsy Materials

The most common diseases leading to heart transplantation are nonischemic cardiomyopathy (50%) and ischemic diseases in adults (1/3). In infants, approximately 50% of the cases of congenital heart diseases and 40% of the cases of cardiomyopathy cause organ loss. Cardiomyopathy is the most common cause of organ loss in 60% of older children. In developed centers, 1-, and 5-year survival rates are 81%, and 69%, respectively. Endocardial biopsies are the gold standard for assessing heart transplant complications. With the transjugular approach, the right heart is approached, and sampling is made from the interventricular septal region. Since the lesions are not diffusely distributed in rejection, at least 3-4 samples are taken. Biopsies per protocol are performed at the time of transplantation to exclude myocarditis, ischemic injury, and other causes. Follow-up protocol biopsies are performed once a week in the first month, every 2 weeks in the second month, and every 4 to 8 weeks between 3-12 months. Evaluation is done according to the International Society of Heart and Lung Transplantation-Working Formulation (ISHLT-WF) system. Cardiac transplant rejection types were divided into humoral and cellular rejection categories in 2011 as was done in other organ transplants. This system was last updated in 2013. In order to be able to say that sufficient biopsy material is obtained for classification, at least 3 specimens should be obtained, and >50% of at least one specimen should contain myocardial tissue. Insufficient number of biopsy specimens, or specimens containing only endocardial tissue, thrombus, previous biopsy site scar or adipose tissue prevent proper histopathological evaluation[1-3,21,22].

Bacterial and viral agents are responsible for the majority of infectious complications, followed by fungal, and parasitic agents. *Toxoplasma bradyzoites* can be observed in sarcoplasmic cysts. Viral inclusions are found in capillary endothelial or perivascular cell nuclei rather than muscle cell nuclei. The presence of adipocytes together with cuboidal mesothelial cells in biopsy materials indicates myocardial wall perforation. Fat tissue alone is not diagnostic. Since adipose tissue is a component of the epicardial layer, fat tissue can also be found in the endocardium in obese individuals

and steroid users. However, if biopsy material contains mesothelial cells, then the biopsy material is taken from the epicardium. It is also possible to see dystrophic calcifications that fill the entire muscle cell cytoplasm.

Quilty effect is a condition that was first described by the surname of the patient and is characterized by the presence of lymphoplasmacytic infiltration in the endocardium. Although cyclosporine has been claimed to have an effect, this issue has not been proven. It is seen in 69% of children and 49% of adults who underwent heart transplantation and is considered an insignificant finding[1,2].

For the diagnosis of antibody-mediated rejection, complement dissociation/degradation products are examined. The presence of C3d and C4d complements is important for the establishment of diagnosis. Serum concentrations of firstly C3, then C4 rise. HLA-DR, fibrin and Igs are unreliable diagnostic parameters. As an important criterion, myocardial capillaries should be stained all around for C3d and C4d. CD68- positive macrophages can be found in the interstitium. However, the presence of CD68 (+) macrophages in myocardial capillaries is an important parameter[1,2]. Cardiac allograft vasculopathy is not specific to the heart and can be seen in all organs. It may be confused with atherosclerosis. It may develop in a few months, or it may take years to develop. It is characterized by intimal proliferation and unlike atherosclerosis, the elastic internal lamina is intact[22].

3) Evaluation of Lung Biopsies

Success rates in lung transplantation have increased within the last 20 years. Bilateral transplantation is performed in most cases. According to the latest data, the average recipient survival time is 5.5 years. For those who survived the first year, survival time extends to 7.7 years, while 5-year survival rate in these cases is 53%. The longest survival time is 7.1 years in cystic fibrosis cases, and the shortest one is 4.3 years in cases with idiopathic pulmonary fibrosis. Today, 3-month, and 1 -year survival rates have increased from 81% to 90%, and from 70% to 81%, respectively[1,2,21].

Three types of early-onset complications may develop after lung transplantation. Primary graft dysfunction develops due to severe ischemia-reperfusion injury. Like acute respiratory distress syndrome, it is the most important cause of post-transplant mortality and morbidity. Survivors often develop bronchiolitis obliterans. Hyperacute rejection occurs when preformed DSA levels are increased, and these antibodies rapidly attack the organ allograft. Antigen-antibody complexes bind to the endothelium, activating complement and causing massive vascular injury in the lung. Since immunological compatibility between donor and recipient is typically not an issue, this is a rare complication. The incidence of airway complications has decreased with the improvement of surgical techniques (7-18%). The rapamycin derivative sirolimus can be a common causative agent. These complications do not develop due to steroids. Necrosis secondary to ischemia and reparative mucosa manifesting as squamous metaplasia are observed[1].

Acute cellular rejection has a frequency of 36-55% in the first year. It is characterized by the presence of lymphocytes around the epithelium and vessels. The detection rate with bronchoscopic biopsy is 80%. For evaluation, at least 5 pieces of lung tissue with alveoli must be examined and at least 100 alveoli must be evaluated. The grading system proposed by The ISHLT-WF is also used for grading lung transplantation biopsies. The existence of acute antibody-mediated rejection for the lung is still controversial. Donor-specific antibodies must also exist. But it is unclear how C4d will be evaluated. Findings are confused with infection, acute cellular rejection, preservation injury and many other conditions[1,21-23].

Chronic lung allograft dysfunction develops in 50% of 5-year transplants. Lymphocytes that cause airway inflammation in cases of acute cellular rejection can lead to mucosal damage and ulceration, along with granulation tissue. This process may occur within a few months following transplantation though it usually develops after 16-20 months. There is patchy involvement. Fibrotic tissue is characterized by type III collagen. Perioperative infections may be caused by actinomyces, staphylococci, and pseudomonas. Most infections that develop in the first month after transplantation are of bacterial origin. Between 1 and 6 months after transplantation, the incidence of bacterial infections decreases, while that of opportunistic infections increases. After 6 months, viral infections may develop and lead to a more severe course. Mycoplasma infections may also occur[1,2,23].

Sarcoidosis is the most common primary disease that relapses. Since cancer can also recur, the presence of carcinoma is a contraindication for transplantation. However, those with 5-year disease-free survival are included in the transplantation list[1,2].

4) Evaluation of Intestinal and Multivisceral Transplantation Biopsies

Transplantation may be performed as isolated intestinal transplantation, or as total/multivisceral (stomach, small and large intestine, liver, pancreas, and spleen) transplantation. Some studies report better results with total transplantation. A very small proportion of intestinal transplantation is performed from a living donor. Potential complications that may develop after intestinal transplantation are acute and chronic rejection, infection, post-transplant lymphoproliferative disorder (PTLD), GVHD, renal dysfunction, bowel perforation, anastomotic leakage, and pancreatitis. Histopathological evaluation should be performed in consideration with the patient's history, clinical findings, and previous biopsy results whenever possible. One or 2 biopsies should be taken from each region and since the lesions are not diffusely distributed, sections obtained from different levels should be examined. GIS transplants should be urgently performed since many posttransplant complications can rapidly lead to allograft dysfunction and failure[1,2].

Preservation damage develops due to ischemia-reperfusion injury. In the early period in a mild lesion, congestion and dehiscence of the surface epithelium are observed in the absence of significant inflammation, edema and swelling of the villi. In its more advanced form, mucosal hemorrhage and deep epithelial necrosis are observed. Findings in the stomach are not well defined[1-3,8].

Clinical and endoscopic correlation is very important for the recognition of acute rejection. Relevant symptoms include increased stool output from the stoma, bloating, and fever. But all these findings are also caused by infections. Morphologically detected rejection without clinical findings is called subclinical rejection[1].

Antibody-mediated rejection: Hyperacute and accelerated acute rejection develop in a few hours or days after transplantation dependent on the presence of high levels of DSAs. Significant bleeding, PMN margination around the vessels, and vascular congestion are seen. Vasculitis can be a very important finding, but it is not usually seen in superficial mucosal biopsies. However, all these listed findings are also observed in ischemia, nonspecific infections and mechanical vascular problems. Therefore, the presence of immunohistochemically detected accumulation of Igs along the interstitium or vessels, and also accumulation of C4d and C3d along small capillaries, and arterioles are important criteria.

Scoring is done as follows[1,2]:

0: Lack of any significant congestion and extravasation.

1: Changes involving 10-40% of the entire tissue obtained.

2: Changes involving 40-70% of the entire tissue obtained.

3: Changes involving more than 70% of the entire tissue obtained.

Acute T cell-mediated (cellular) rejection is the most frequently encountered form of acute rejection in all gastrointestinal and visceral organ transplantations. Lymphocytes play the leading role. Lymphocytes target crypts, glandular structures as well as muscle, endothelial and even nerve cells. Parenchymal metaplasia is observed. CD4- and CD8- positive cells, more often cytotoxic T lymphocytes underlie acute cellular rejection. Apoptosis of crypt epithelial cells is the most common change. CD8 (+) T cells lead to apoptosis via granzyme B/perforin-dependent granular exocytosis pathway FAS/FAS-L dependent cytotoxicity. In animal models, cells other than cytotoxic T lymphocytes have been shown to contribute to apoptosis of crypt epithelial cells. In the grading system, the most important finding is the presence of apoptotic body. The presence of less than 6 apoptotic bodies in 10 crypts is not considered a rejection. In severe acute cellular rejection, extensive morphological distortion, gland destruction, granulation tissue formation with widespread presence of neutrophils and eosinophils, and mucosal peeling with fibrinopurulent exudate are observed. Infections should always be considered in the differential diagnosis of acute cellular rejection. However, as an important corollary concerning differential diagnosis, apoptosis does not increase even in severe infections. The same grading system is also used in the evaluation of rejection in small intestine transplants containing a colonic segment. In gastric transplantation, the grading is slightly different[1-3,8,24,25].

Chronic rejection is also known as chronic allograft enteropathy. In this case, treatment-resistant, progressive protein-losing enteropathy occurs. In endoscopic examination, loss of villi is observed. Pathognomonic findings of chronic rejection are intimal thickening of arteries, medial hypertrophy and adventitial fibrosis. Since mucosal biopsy materials generally do not contain large vessel architecture, mucosal biopsy has a limited diagnostic value. The presence of chronic injury characterized with fibrosis, crypt loss, distortion,

and architectural changes associated with clinical and endoscopic findings may indicate chronic rejection[1-3,24,25].

5) Evaluation of Liver Transplantation Biopsies

While the most common indications for liver transplantation in the USA are HCV infection, alcoholic and non-alcoholic steatohepatitis, chronic HBV infection still predominates in Asia. Ideal donors are deceased persons under 40 years of age, with brain death due to trauma, without cardiovascular, chronic liver disease, and steatosis, but with intact circulation until the time of transplantation. Use of significantly macrosteatotic (>40%) cadaveric organs, those exposed to cold ischemia for more than 12 hours, or organs taken from deceased individuals over 60 years of age are more often contraindicated for transplantation. Living donor transplantations carry a risk of 0.2% mortality and 25% morbidity. Complications following transplantation include vascular complications such as preservation (ischemia/reperfusion) injury, portal hyperperfusion or small allograft syndrome, hepatic artery thrombosis, portal vein thrombosis, hepatic vein and vena cava complications, and biliary tract complications[1-3].

Rejection in the liver is generally considered as acute antibody-mediated rejection, T-cell-mediated rejection, and chronic rejection, as in other solid organ transplantations. The liver is more resistant to antibody-mediated rejection associated with anti-MHC 1 and 2 antibodies compared to the lung and heart. Antibody-mediated rejection usually develops in the first few weeks after transplantation in cases with incomplete ABO compatibility. There is a high titer of DSA in the circulation. Since full ABO compatibility in liver transplantation is only required in the USA, and other countries in the American continent, antibody-mediated rejection is observed more frequently in Asian countries. Hyperacute perfusion can also be seen in the liver which develops following a bleeding episode. In acute rejection, levels of serum bilirubin and parameters of liver function tests rise within a few days or weeks following transplantation. Although it is difficult to distinguish this condition from preservation damage and biliary stricture, increased isoagglutinin levels and C4d staining aid in diagnosis. The O'Leary criteria, updated in 2014, are used for grading acute antibody-mediated rejection. The diagnosis of chronic antibody-mediated rejection is somewhat more uncertain. However, as a rule, signs of acute antibody-mediated rejection should be accompanied by fibrosis, which is a sign of chronic injury[1,2].

Early (<6 months) onset T-cell-mediated rejection affects approximately 30% of cases and develops 5-30 days after transplantation. Risk factors include type of immunosuppressive therapy, being young and healthy (child N, creatinine N), HLA-DR incompatibility, autoimmune hepatitis in the recipient, primary sclerosing cholangitis-like immune deviations, prolonged cold ischemia, elderly donor, and HLA-C genotype. It rarely causes allograft failure or permanent damage and responds well to treatment. Late onset (>1 year) type is usually associated with inadequate immune suppression, DSA development, and can lead to organ failure. It is somewhat similar to chronic hepatitis with a late onset associated with a slightly lower number of blastic lymphocytes, increased interface and lobular activity, milder venous subendothelial but more intense perivenular inflammation. As a rule, in T cell-mediated rejection (especially in the early-onset type), mixed portal inflammation consisting predominantly of activated/blastic lymphocytes, subendothelial inflammation (endothelialitis) in the portal or terminal hepatic venule, and bile duct inflammation-damage must be present. A majority of the lymphocytes are of the CD8 phenotype. The BANFF grading system also indicates the severity of the lesion. According to this system, presence of portal inflammation that does not meet the diagnostic criteria of acute rejection criteria is called indeterminate. In mild cases of acute rejection (grade 1), rejection infiltrate is confined only within some portal spaces. In grade 2, it is present in most portal spaces. In grade 3, the perivenular infiltrate extends beyond the portal area is found. In acute rejection, some centers utilize the rejection activity index. Accordingly, all three findings are scored separately[1-3,26,27].

Signs of chronic rejection include ductopenia, obliterative arteriopathy and perivenular fibrosis. Typical chronic rejection can be defined as early or severe. It causes permanent damage to bile ducts, arteries and veins. Previously, signs of chronic rejection had developed in the first years after transplantation. While the rate of chronic rejection was 15-20% in a 5-year transplant in the 1980s, today this rate has decreased to 3-5%. It is mostly seen in patients who are transplanted without full histocompatibility, HCV (+) patients who are receiving immune activator therapy such as interferon alpha, and those whose immunosuppressive dose is reduced due to lymphoproliferative disease. Risk factors are considered in 2 groups as alloantigen-related and non-alloantigen-related. The most important non-immunological risk factor is the donor age above 40 years[1,2,26-28].

6) Evaluation of Pancreas and Pancreatic Islet Transplantation Biopsies

Pancreas allograft transplants are most commonly performed in type 1 diabetes where hypoglycemia attacks cannot be controlled with ensuing progression of vascular and renal complications. Some pancreas and kidney transplantations are applied synchronously. Only 5-6% of the cases are type 2 diabetes patients. A very small group have a large benign tumor or a dysfunctional organ due to recurrent chronic pancreatitis. Organ or islet autotransplantation should be considered, especially when organ removal is required due to the presence of a benign tumor[1,2].

The first pancreas transplantation was performed in 1966, and the patient lived for a week without the need for insulin, but died in the second week due to pulmonary embolism secondary to pancreatic fistula and pancreatitis-like complications. Many methods have been tried for the drainage of the exocrine pancreas. While only 100 pancreatic transplantations were reported in the world until 1980, this number increased to over 30 thousand in the early 2010s. In the previously tried technique venous drainage was diverted into the iliac vein and exocrine secretion into the native duodenum. Eventually, drainage of exocrine secretion into the bladder was predominantly utilized. Despite side effects of this application, such as hematuria, urinary leakage, recurrent infection, it is useful in monitoring of urine amylase levels. Indeed a decrease of more than 25-50% in post-implant amylase levels is indicative of rejection. Nowadays, enteric drainage is preferred due to its suitability for the physiological condition, and the portal system or iliac vein is used for venous drainage. Elevated creatinine levels in synchronous pancreas and kidney transplants is a finding suggestive of rejection. The increase in amylase-lipase-like exocrine pancreatic enzymes in the blood is an indicator of exocrine acinar cell damage and the levels of these enzymes increase in rejection. However, they are also elevated in inflammatory conditions such as acute pancreatitis. Similarly, hyperglycemia is also seen. Today, less than 10% of successfully transplanted pancreas is lost to acute rejection. However, 5-year organ survival rate is around 40-50%[1,2,29-31].

The diagnostic sensitivity of biopsy in acute rejection is 80%. Due to the non-specific nature of laboratory tests, needle core biopsy is the gold standard diagnostic method for acute rejection. Ultrasonography or computed tomography-guided percutaneous needle biopsy technique was first used in the 1990s, and sufficient biopsy material can be obtained in 85-90% of cases. The rate of serious complications such as bleeding is 2-3% which does not cause organ loss. However, intestinal loop may prevent percutaneous biopsy in patients who are undergoing intestinal drainage. In these cases, laparoscopic biopsy can be performed. In patients undergoing bladder drainage, cystoscopic biopsy can be performed instead of percutaneous core biopsy. The rate of obtaining sufficient tissue specimen with this technique has been reported to be between 57-80%. However, this method is more invasive and expensive. It has been reported that in patients who have recently undergone enteric drainage, pancreatic graft tissue has been found in the proximal jejunum, which is the site of anastomosis, and sufficient material is sampled in 75% of these cases. It is recommended that the biopsy specimen should contain at least 3 pancreatic lobules with accompanying interlobular spaces.

Typically, veins, branches of the pancreatic ducts, and arterial branches are observed in the interlobular space. For best results, at least 2 H&E stained sections from different levels should be examined. All biopsy specimens should be subjected to C4d staining. Humoral rejection should be considered, especially in cases where hyperglycemia develops without any other finding in biopsy or if there is interacinar capillary margination of PMN and other inflammatory cells. Insulin and glucagon staining are also required to demonstrate selective beta cell loss due to recurrence of an autoimmune disease in patients undergoing biopsy for hyperglycemia. Animal experiments have shown that renal and pancreatic transplant rejections coexist in most of the cases (65%). However, their rejection rates can be different. In a large series, the pancreas was singularly rejected in 22% and only the kidney in 13% of the cases. Therefore, it is recommended to perform separate biopsies. Controversial results have been reported regarding the benefit of protocol biopsies and accelerated treatment applied when rejection is detected[1,2,29-31].

Acute allograft rejection mechanisms in pancreas transplantations are not different from those observed in other solid organ transplantations. MHC class I and II molecules are expressed differently in different regions of the pancreas. Normally MHC class II molecules are not involved in this rejection. MHC class I molecules are expressed strongly in the ductal epithelium and weakly in the islets. They are not expressed in normal acinar cells. In acute rejection, acinar cells show overexpression of both MHC class I and II cells. MHC class

II overexpression is also observed in ductal epithelium and endothelium, while MHC class I is only seen in beta cells. The leading cells in cellular rejection are T lymphocytes, monocytes and eosinophils. Cytotoxic T lymphocytes exert their function via perforin, granzyme-like enzymes and FAS ligands. In antibody-mediated rejection, antibodies accumulating on the vessel wall directly stimulate the complement cascade or antibody-dependent cell-mediated toxicity, leading to vascular injury, necrosis, thrombosis, and parenchymal necrosis. Hyperacute rejection, which is a much more severe reaction, also occurs by a humoral mechanism, as described previously. Various rejection patterns develop dependent on different patterns of MHC distribution, and vascularization as well as resistance to ischemia. Animal experiments have shown that the main target of T cell-mediated rejection is the acinar lobules. In chronic rejection, there is fibrosis caused by chronic vascular injury. Islet cells are not directly affected by T cell and antibody-mediated rejection[1,2].

Studies in animal models have shown that acute rejection progresses with inflammatory infiltration in the interstitium, which also involves heterogeneous small vessels and ducts. Acinar inflammation and acinar cell apoptosis may be also observed. More severe forms include intimal arteritis, necrotizing vasculitis, thrombosis with gradual formation of parenchymal necrosis. Although islets of pancreas are not on target, hyperglycemia occurs because islets are affected by extensive parenchymal necrosis. A six-level grading system originally developed by the University of Maryland was used to evaluate pancreatic transplantation pathology. However, this grading system was not successful in the evaluation of the pancreatic transplantation pathology due to the similar histopathological features of grades 2 vs 3 and 4 vs 5. Today, the Banff grading system, which was updated in 2011, is used[1,2,29-31].

FOREMOST DIFFERENCES BETWEEN SOLID ORGAN TRANSPLANTATIONS PERFORMED IN CHILDHOOD AND ADULTHOOD

When the data collected from transplantation centers all over the world are reviewed, an annual increase of approximately 6% is observed in the number of solid organ transplantations from the beginning of the century until 2020. However, solid organ transplantations decreased approximately 17.5% in 2020 due to the impact of the coronavirus disease-2019 pandemic. According to the data of the World Health Organization, more than 150,000 transplants were performed all over the world in 2019 and more than 130,000 in 2020. It is thought that these figures constitute less than 10% of the cases in need of organ transplantation. Mostly kidney (37%) and liver transplants (21%) have been performed. The proportion of pediatric cases receiving solid organ transplants is quite low[32].

The pediatric liver transplant rate has remained stable over the past 5 years. Most liver transplants are from deceased donors, with childhood liver transplant rates reported as 5-6% in North America, 11% in Europe and 17% in Australia. In contrast, 35% of all liver transplants in Japan were performed on children, and almost all were performed from living donors. In a study in which Ege University liver transplant cases from Turkey were presented, the pediatric transplant rate was 18.7%, and it was stated that more than half of the transplants were from living donors, especially after 2000[28,32-34].
Liver transplantation has been very successful in the treatment of children with end-stage liver disease and has provided many years of disease-free survival. Donor shortage, which is the main limitation of transplantation, has been overcome due to innovative surgical techniques such as split-liver or living-donor transplantation. Today, organ transplantation is performed in pediatric cases with almost no waiting list mortality. While formerly the focus of care for children with end-stage liver disease was to perform liver transplantation, today the main aim is to prevent complications related to immunosuppression and to ensure normal growth[35].

In the first years of kidney transplantation, lower graft and patient survival rates were reported in pediatric cases compared to adult cases. In the last 20 years, the success rates have increased considerably, and the 5-year survival rates have been reported as 94% in pediatric renal transplantations from a living donor, and 77-85% in deceased donor transplantation. Many studies have reported that graft survival in pediatric cases is lower than in adults, secondary to poor adherence to drug regimens, side effects of drugs, and a higher rate of recurrent disease. However, it is reported that no difference is observed in terms of patient survival between adult and pediatric kidney transplantations.

Although the clinical process is similar in pediatric and adult patients, the causes leading to end-stage organ failure differ in several aspects, such as the types of complications, optimal donor selection, growth-related problems, associated comorbidities, adherence to drug regimens, and their effects on growth and

development. While the causes of kidney failure in adults are usually diabetic nephropathy, hypertension, autosomal dominant polycystic kidney and chronic glomerulonephritis, the causes of kidney function loss in pediatric patients are mostly FSGS, renal dysplasia and urological disorders due to urinary system anomalies. In addition, recurrent glomerulonephritis in allografts, especially recurrent FSGS is more commonly seen in pediatric patients, and it is an important complication that determines the long-term outcome of the transplant[5,33].

Cardiovascular complications are among the most important complications following pediatric kidney transplantation, and cardiovascular mortality in children is 100 times higher than age-adjusted healthy pediatric population. Cardiovascular disease accounts for 11% of the causes of death after kidney transplantation in pediatric patients. Various metabolic conditions that develop during dialysis, such as obesity, hyperglycemia, hypercholesterolemia, and hypertension, tend to persist after transplantation. In addition, donor-recipient size mismatch is an important factor that increases the pathological cardiac burden in pediatric lung transplantation. Pediatric donors are few among the donor population and pediatric donors are not always suitable as pediatric recipients due to the technical difficulties of anastomosis with small vessels and the risk of thrombosis at the anastomosis site. Therefore, in pediatric patients the kidney is usually obtained from adult donors and donor-recipient size mismatch is a common challenge, especially in infants and young children. Donor-recipient size mismatch usually results in graft hypoperfusion and delayed graft function[5].

Heart transplantation is a valid treatment for end-stage heart disease in both adults and children. Survival after heart transplantation from birth to the age of 18 is excellent, and this rate is reported to be over 65% for all age groups[6]. Although survival rates in pediatric cases are comparable to those of adults, there are important differences regarding indications, assessment, surgical technique, and post-transplant management. Indications for transplantation in pediatric patients include metabolic and genetic diseases leading to cardiomyopathy and congenital heart disease. Since mitochondrial and metabolic diseases are among the etiological factors, during the evaluation process, metabolic examinations should also be done. In the presence of phenotypic features of genetic anomalies or family history, genetic studies should be performed. Most importantly, if children referred for transplantation due to congenital heart disease had previously undergone multiple palliative surgical interventions, then the success of pediatric heart transplantations is reduced. The main problems to be experienced in pediatric cases after heart transplantation are the inadequacy of education and social support, the disruption of growth and development, and the need for psychosocial assistance of the patient and family in relation to their future expectations[6].

Wever-Pinzon et al.[22] investigated 52,995 heart transplantations and reported that the causes of death differed significantly with the age of the recipient at the time of transplantation. The lowest ten-year survival rates were found in patients aged 60 to 69 years (49%), and ≥70 years (36%). Whereas, acute rejection, cardiac allograft vasculopathy and graft failure were observed at high rates in the youngest patient group. While the risk of death due to infection and malignancy was high in elderly recipients, the risk of death from renal failure was low in young recipients. Cause-specific death profiles in this study suggested the possible impact of inadequate immunosuppression in younger and excessive immunosuppression in older recipients. Since there was no pediatric case in the study, no comment was made on cause-specific mortality rates[22].

Lung transplantation in children has been performed since the 1980s. Currently, pediatric lung transplantation has provided a clear survival advantage and improved quality of life in well-selected children with end-stage lung disease[1-3]. It has been reported that over 100 pediatric lung transplants are performed worldwide each year, and over 2400 procedures have been performed in children to date. However, the number of centers performing pediatric lung transplantations have remained almost unchanged in recent years. Conventionally, centers performing pediatric lung transplants are mostly located in North America, Europe, and Australia, although successful cases of pediatric lung transplants have also been reported in Asia and South America. Cystic fibrosis remains the most common primary indication for pediatric lung transplantation, although indications vary considerably with patient age. Pulmonary hypertension and surfactant disorders in infants are the main indications. Cystic fibrosis and idiopathic pulmonary hypertension are the most common indications for lung transplantation in children aged one to 10 years. In adolescents (11-17 years of age), cystic fibrosis is by far the most common disease leading to lung transplantation, especially in centers outside of North America. However, just like other

solid organ transplantations, the surgical approach in lung transplantation is more challenging in children. In addition, the effects of immunosuppression on the developing immune system in these patients and its psychosocial effects, especially in adolescents, should be considered[1-3,36].

Growth retardation is a common problem in pediatric patients after solid organ transplantation. It is known that the growth and development of living related donor kidney recipients is better than that of cadaveric donor graft recipients. In pediatric renal transplantation, transplantation before 6 years of age, refraining from steroid treatment and use of recombinant human growth hormone (rhGH) have positive effects on growth of these children. However, the use of rhGH was found to be associated with an increased incidence of renal cell carcinoma and acute rejection in patients with a history of acute rejection[5].

Almost 75% of adolescents tend not to comply with treatment regimens, and this is an important factor that can lead to organ loss in pediatric transplants. In general, a child's transition to adulthood is a very labile period, and while the rate of one-year survival after transplants made during this period is very good, long-term transplant results have been disappointing. Non-compliance with the use of immunosuppressive drugs is one of the most important factors contributing to graft rejection and loss in adolescents. Therefore, adherence to treatment should be monitored with objective methods such as close monitoring of blood levels of drugs and extensive use of electronic devices[5].

PTLD is an abnormal lymphocyte proliferation seen in immunocompromised patients receiving transplantation. Histopathological findings range from infectious mononucleosis-like disease to the development of non-Hodgkin lymphoma. Since a longer posttransplant survival is expected in pediatric cases, PTLD poses a crucial challenge. Risk factors for PTLD include EBV seronegative status of recipients, use of calcineurin inhibitors and antilymphocyte antibodies, number of methylprednisolone pulses administered, presence of CMV infection, young age, and acute graft rejection events. While the incidence of PTLD in adults is 1%, it has been reported up to 49% in EBV-seronegative pediatric patients. The risk of non-PTLD malignancy in kidney transplanted children was also found to be 6.7 times higher than in a healthy pediatric population. Renal cell carcinoma is the most common type of non-PTLD malignancy observed[5,32-34].

CONCLUSION

In summary, solid organ transplantation performed in children differs from adults in several aspects including clinical features, causes of organ loss, types of complications, selection of optimal donors, growth problems, drug incompatibility, transition to adulthood, and effects on the child's development. Therefore, for the success of pediatric organ transplantation, a multidisciplinary approach with effective intra-and inter-institutional coordination between pediatricians and pediatric subspecialists, gastroenterologists, cardiologists, pulmonologists, urologists, transplantation surgeons, immunologists, pathologists, social workers, pharmacists, and clinical coordinators conveys critical importance.

Ethics

Peer-review: Internally peer reviewed.

Author Contributions

Surgical and Medical Practices: P.R., G.D., Concept: P.R., G.D., Design: P.R., G.D., Data Collection or Processing: P.R., G.D., Analysis or Interpretation: P.R., G.D., Literature Search: P.R., G.D., Writing: P.R., G.D.

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