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IMMUNOLOGICAL ASPECTS OF THE CYTOMEGALOVIRUS INFECTIONS AFTER PEDIATRIC LIVER TRANSPLANTATION

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Conflict of interest
The authors declare that they have no conflicts of interest

Abstract

CMV infection is one of the most common infectious complications of viral etiology among both adult patients and children after liver transplantation. Our experience shows that the appointment of preventive therapy led to a decrease in the frequency of indirect effects of CMVI, and also improved the survival rates of patients after transplantation. This article describes in detail the immunological changes in the background of CMV infection and immunosuppression.

Keywords
Cytomegalovirus, immunosuppression, antibodies, valganciclovir, liver transplantation

Бауыр трансплантациясынан кейінгі балалардағы цитомегаловирустық инфекцияның иммунологиялық аспектілері

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Мүдделер қақтығысы
Авторлар мүдделер қақтығысының жоқтығын мәлімдейді.

Аңдатпа

ЦМВ инфекция ересек науқастар арасында да, бауыр трансплантациясынан кейінгі балалар арасында да жиі кездесетін жұқпалы асқынулардың бірі болып табылады. Біздің тәжірибеміз профилактикалық терапияны тағайындау ЦМВ инфекцияның жанама әсерлерінің жиілігін төмендетуге, сондай - ақ трансплантациядан кейін пациенттердің өмір сүру деңгейін жақсартуға әкелгенін көрсетеді. Бұл мақалада ЦМВ инфекция мен иммуносупрессия кезіндегі иммунологиялық өзгерістер егжей-тегжейлі қаралған.

Түйін сөздер
Цитомегаловирус, иммуносупрессия, антиденелер, валганцикловир, бауыр трансплантациясы

Иммунологические аспекты цитомегаловирусной инфекции у детей после трансплантации печени

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Конфликт интересов
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Аннотация

ЦМВ инфекция является одним из самых частых инфекционных осложнений вирусной этиологии как среди взрослых пациентов, так и среди детей после трансплантации печени. Наш опыт показывает - назначение профилактической терапии привело к снижению частоты непрямых эффектов ЦМВИ, а также улучшило показатели выживания пациентов после трансплантации. Данная статья детально отражает иммунологические изменения на фоне ЦМВ инфекции и иммуносупрессии.

Ключевые слова
Цитомегаловирус, иммуносупрессия, антитела, валганцикловир, трансплантация печени

Topicality

The cytomegalovirus (CMV) is one of the most frequent virus agents having an influence on the results of hepatic transplantation. The cytomegalovirus (CMV) is widespread both among the patients in the condition of long-term medicamentous prophylactic suppression and among the population in general (60-100%). It is the main risk that can cause the loss of the transplant and the death of the patient after fulfillment of the hepatic transplantation. Decrease in the quantity of similar complications by means of various methods of prevention was demonstrated in the two meta-researches. According to the information received, HCMV develops within the first year after hepatic transplantation fulfillment without use of preventive antiviral preparations approximately in 44–65% of the cases.

Aim

The appraisal of the role of the cytomegalovirus infection in case of pediatric transplant immunology and CMV influence on the results of hepatic transplantation. The main methods of fight against this infectious complication are widely described in the world literature, but these publications are generally related to adult hepatic transplantation. The researches in the field of pediatrics have limited character.

Materials and methods

Thirty (30) surgery operations on pediatric hepatic transplantation have been fulfilled since March, 2016 with use of the materials taken from live kin donors. The age of the patients: 6 months - 8 years old, as follows: 23 (76.6%) patients - Biliary Atresia; 2 (6.9%) patients - Hepatic Cirrhosis in the outcome of autoimmune hepatitis; 1 (3.3%) patient - Primary Hyperoxaluria; 1 (3.3%) patient – Cholangiocarcinoma; 1 (3.3%) patient - Inoperable Hepatoblastoma; 1 (3.3%) Hepatic Cirrhosis in the outcome of Viral Hepatitis «C» against the background of langerhans cell histiocytosis. The number of the female infants - 17 (56.7%) patients and the male infants – 13 (43.3%) patients.

Results

All the patients with the positive quantitatives PCR took Cytomegalovirus immunoglobulin 3-5 before the operations. The left lateral sector was transplanted to the 23 (76.6%) patients with biliary atresia from their CMV seropositive kin intravital donor (D+/R+) and the 4 (23.3%) patients – from their CMV seronegative donors (D-/R+). The total number of the seropositive donors (D+/R+) - 26 ones (86.6%). The total number of the seronegative donors (D-/R+) – 4 ones (13.4%). One Simultaneous Liver-Kidney Transplantation was fulfilled for one infant patient. All the patients with biliary atresia had CMV infection. Eight (8) patients had an active form of the disease. The follow-up period: 14 days – 3 years after transplantation. The ternary phylactic suppression therapy was fulfilled after each operation -Prednisolone, Cell-Cept, Tacrolimus. Activization took place in 3 (12%) patients with a not active form of CMV. The neurologic symptoms were in progress in 2 patients. The active CMV form in 1 patient was connected with the toxic effect of the fulfilled phylactic suppression therapy (Tacrolimus). The preparation had to be discontinued temporarily to stop the intoxication and the conservative methods and preparations were prescribed for the patient. All the patients with CMV infection took antiviral therapy with the preparation Valganciclovir (18 mg/kg) for a month and the viral load was decreased in the patients with the active form of CMV. Six (6) months later the quantitatives PCR for CMV became negative in all the patients. Nine (9) months later the viral load increased in 1 (3.3%) patient with the not active form of CMV. Twelve (12) months later Viremia was diagnosed in 6 (20%) patients and they were prescribed the antiviral therapy during the period of 3-6 months with Valganciclovir. Decreasing the total number of T-lymphocytes and T-helpers was registered against the background of phylactic suppression therapy and viremia (8 patients).

The imbalance was revealed in the content of the main subpopulations of T-lymphocytes (CD3+CD4+/CD3+CD8+ = 1:65) and activation was increased (CD3+CD25+ = ± 8.59%) in 50% of the patients against the background of the decreased total number of T-lymphocytes (CD3+ CD4+ = 30.34% and CD3+ CD8+ = ±18.3%) of the main subpopulations of T-lymphocytes (CD3+CD4+ =±18.3%). The insignificant proliferation of B-lymphocytes (30-44%) was marked as well. The cause of the revealed changes in the cellular level may be the immunodeficiency induced with the presence of a center of not-acute inflammatory process. Three (37.5%) patients had the following level of lymphocytes: CD3+ = ± 60.39%. The expressed imbalance in the main subpopulations of T–lymphocytes was revealed as well: (CD3+CD4+/ CD3+CD8+ = ±0.99). It was conditioned with decreasing the content of the helper subpopulation of T–lymphocytes (CD3+CD4+ = ±30.59%). The level of the lymphocytes of the late activation was increased - (CD3+ HLA - DR + = ±9.29%) as well as the level of the T-NK cells - (CD3+CD (16+56) += 7.15%. The content of the B-lymphocytes (CD19+ = 24.73%) and NK-cells (CD3-CD (16+56) += ±13.87%) was within normal range. The expressed immune imbalance was marked because of using

the phylactic suppression therapy and presence of a CMV-disease or CMV Viremia. The higher the concentration of the phylactic suppression therapy was, the higher the CMV-titres in the blood became. The following serological researches were fulfilled for all the patients: Definition of the IgM and IgG antibodies both with the CMV methods and the methods of Enzyme Immunoassay as well as the definition of DNA of CMV in the blood and Liver Biopsy Slide with the method of PCR. The positive result of any abovementioned tests (the antibodies IgM and IgG with low avidity, the DNA of CMV in the blood and in the tissues and also specifical inclusions in the LBSs) was considered as a case of a CMV-infection.

Conclusions

Practical recommendations:

1. The main prophylaxis of the CMV infection has to become the combination of the monitoring of the activity of the infection process with a long-term medicamental prophylaxis and treatment of all the episodes of the active CMVI.

2. Prescribing the pulse-therapy in case of rejection of the hepatic transplant it is necessary to take into account the character of the running of CMVI and apply the antiviral prophylaxis with Valganciclovir or Ganciclovir as needed as well as to fulfill all the necessary researches of the CMV activity in the plasma of the blood with PCR method.

3. It is recommended to prescribe a double medical dosage of Ganciclovir, Valganciclovir and human normal immunoglobulin, immunoglobulin against CMV and also decrease of the level of medicamentous phylactic suppression or its temporary cancellation in case of resistance of CMVI to basic therapy.

4. The liver recipients may be used the above mentioned immunoglobulins to correct the immune imbalance taking into account the immunodeficient condition caused with the phylactic suppression therapy.