CYTOMEGALOVIRUS INFECTION AFTER KIDNEY TRANSPLANTATION, SUSCEPTIBILITY TO CMV-INFECTION IN ASSOCIATION WITH HLA-GENOTYPE

Doctoral thesis

MARINA VARGA MD

Semmelweis University
Clinical Medicine Doctoral School

Supervisor: György Reusz MD, PhD, DSc

Opponents: Rozália Pusztai, MD, DSc
            István Mucsi MD, PhD

Head of the exam committee: Ilona Kovalszky MD, PhD, DSc
Members of the exam committee: László Szőnyi MD, PhD
                               Pécsiné Éva Barabás PhD

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Introduction

Immunosuppression is a necessary procedure in order to prevent the graft-organ from rejection after organ transplantation. But this method could have disadvantageous consequences: the immunosuppressive medication depresses the immunity of the recipient, and it will not attack the graft, but at the same time it will fail protect the organism against the infections. In the early historical era of the transplantations it was clear that infections following organ transplantation were becoming one of the major factors determining the fate and survival of patients, due to their high frequency and severity. Infection related mortality among kidney transplant patients is 30% of all mortality: it consists of 35% of sepsis, 22% of bacterial infections, 24% of invasive viral infections and 18% of fungal infections. During the last decade severe infections became successfully treatable due to modern antibacterial, antiviral and antifungal medicine. But it is important to know, that infections in immunocompromised may product unusual symptoms, we have to realize the special infective agents and we have to use the modern diagnostic methods in order to administer the adequate therapy in due time.

Viruses play a special role among infections after transplantation. The immunosuppressive therapy decreases the function of cellular immunity, which is important in protection against viruses from Herpesviridae, Polyomaviridae, Papillomaviridae families. These viruses do not disappear after the acute primary infection, but latently remain in the infected organism for a long period. From time to time the latent viruses reactivate due to proinflammatory triggers. In case of immunosuppression the suppressed cellular immunity is not able to inactivate the hive of viruses, and symptomatic secondary infection develops. The primary viral infection developed under immune suppressed condition usually results more severe symptoms, in the most cases the source of the viruses is the graft-organ from seropositive donor.

Cytomegalovirus (CMV) infection is an important and common complication of solid organ transplantation, which decreases the long-term graft and patient survival. Remarkable progress has been made in understanding of CMV-infection pathogenesis, especially in case of solid-organ transplant patients. The occurrence of severe CMV-infection in transplant patients decreased thanks to modern diagnostics
and effective drug-therapy, but it is important to take in view that the sustained viral effects – even in asymptomatic cases – lead to damage of parenchimal organs, especially of graft-organs. That’s why today it is not enough to treat the CMV-disease but it is important to prevent the primary infection and the viral reactivation in due time. When introduce the preventive therapy, it is recommended to determine the risk factors for CMV-infection and to choose the preventive procedures according to their effectiveness. Over the years I had got an experience with CMV-infection and its diagnostics after kidney transplantation in the Transplantation Centre of Budapest. The aim of this study is to determine CMV-seroprevalence and it's characteristics in Hungarian population, to find a correlation between susceptibility to CMV-infection and genetic predisposition, and to define the optimal diagnostic procedures for acute CMV-infection in solid-organ transplant patients. I’m sure the results and conclusions of this study will be useful in the management of transplant patients.

Aims of the study

1. To collect and analyze data of organ-donors, and drawing appropriate conclusions regarding CMV seroprevalence of Hungarian population, to determine the characteristics of the seroprevalence according to age-, sex- and blood group distribution.

2. To determine the optimal diagnostic procedures for acute CMV-infection in solid-organ transplant patients: comparison of serologic method’s, CMV antigenemia test’s, "shell vial" virus-isolation’s, PCR test’s parameters and applicability. To define the algorithm of procedures for diagnosis of CMV-infection.

3. To compare the effectiveness of CMV-infection prophylactic protocols for high-risk kidney transplant patients according to occurrence and severity of the acute infection, to time between transplantation and infection and according to correlation with rejection.

4. To analyze data of primary CMV-infections of high-risk kidney transplant patients, to find a correlation between susceptibility to CMV-infection and certain HLA-types, the role of the genetic predisposition.
Patients and methods

1. Patients and methods – data analysis of CMV-seroprevalence among donors and elderly, laboratory diagnostic methods.

Patients:
Between 1998 and 2007 data of 2070 organ-donors were investigated: 1278 males (62%) and 792 females (38%). The mean age of the donors was 44.6 years (2-70). The donors were divided into three age-groups: (2-20, 21-50, 51-70 years old). A study was also conducted on a fourth group consisting of 200 residents from an old-age home, age range of them was 71-92 years. CMV seroprevalence of the organ-donors and residents of the old-age home (altogether 2270 persons, age 2-92 years old) was analysed.

Methods:
The CMV seroprevalence was determined by measuring the CMV-specific IgG (ELISA or MEIA methods using commercially available assays: Behring, Abbott). All viral measurements of the organ-donors were carried out in regional centres of the Hungarian National Blood Transfusion Service (HNBTS). The anti-CMV IgG tests for old-age home residents were held in the National Centre for Epidemiology in Budapest. The CMV-seroprevalence differences were searched according to age-, sex- and blood-group distribution.

2. Acute CMV-infection after solid-organ transplantation, methods of the laboratory diagnosis

Most of the modern diagnostic methods derive from the nineties. The most optimal and appreciable methods were chosen according to the comparative studies.

1). Comparison of serologic method, CMV antigenemia test and "shell vial" virus-isolation

Patients:
The study was carried out on 80 transplant patients (kidney, heart and bone marrow) and were aimed on the diagnosis of the acute CMV-infection in case of suspect (suspicious symptoms were fever, leukopenia, malaise, arthralgia, impairment of graft function). For 24 bone marrow-, 50 kidney- and 6 heart transplant patients 645 examinations were carried out in the National Centre for Epidemiology in Budapest. During the follow up the patients’ samples were examined once a week till the
reconvalescence. CMV-infection was defined as detection of at least one of the symptoms and of positivity at least one of the diagnostic measurements. Other possible reasons of the symptoms had to be excluded. For determination of the specificity and predictive values of the methods the samples of 10 other - healthy - persons were also measured.

Methods:
I. Serologic method
CMV-specific IgM and IgG antibodies were determined by an enzyme-linked immunoadsorbent assay (ELISA –Behring, Gull) according to the manufacturer’s prescriptions. The CMV-infection was proved by appearance of CMV-specific IgM antibody, the changing of CMV-specific IgG titre weren’t accept as the sign of the acute CMV-infection.

II. Detection of the CMV Antigen (early matrix protein – pp65) in the leukocytes (antigenemia test)
The CMV antigenemia test was performed by immunocytologic assay for the detection of CMV pp65 antigen (antigenemia test) in circulating peripheral blood leukocytes (PBL) by the use of monoclonal antibodies (Biotest, Clonab) and anti-mouse immunoglobulin (DAKO), the results expressed quantitatively by reporting the number of CMV antigen positive cells per 100 000 PBL.

When the test was introduced, it took 6 hours to carry out the procedures. With the modernization of the method (use of ready-for-use reagents) and with automatization (use of haematology automate for cell counting) the time of the test was shortened to 4 hours.

III. “Shell vial” virus-isolation
For the virus-isolation blood samples were collected.

a). The human fibroblast cell-culture was inoculated with the blood samples through centrifugation. The incubation was hold for 3-4 days on 37°C degrees. The human fibroblast cell-tissue was cultivated in the laboratory of the National Centre for Epidemiology.

b). The inoculated cells were incubated with CMV-antigen specific monoclonal antibodies from manufacturer (Dako) and with home-made antibodies (5D12). After
incubation with FITC labelled anti-mouse immunoglobulin, the results were read with fluorescent microscope.

The occurrence of fluorescent inclusions in the nucleus of the fibroblasts proved that the virus was in the sample and that the patient was infected with CMV (viraemia).

The analysis of the methods

The results of the comparison were analyzed according to following parameters: sensitivity, specificity, positive and negative predictive values.

2). Comparison of the PCR test and CMV antigenemia test

Another prospective comparing study was carried out at the Transplantation and Surgical Clinic. 15 kidney transplant patients (13 males and 2 females) were followed during 6 months after the transplantation. Both of the examinations were hold 6 times after the transplantation: on days 7, 14, 28, 54, 91 and 183, these days were the best according to the patient compliance. The PCR test was carried out according to the manufacturer’s prescription (Cobas Amplicor, Roche). The question was which of these two methods would show earlier the primary CMV-infection or the viral reactivation in the early posttransplant period. The methods were compared according to their sensitivity and specificity. The applicability of the tests was also investigated.

3. CMV-infection in high-risk kidney transplant patients with different prophylactic protocols, patients and methods of the study

Patients:

From January 1997 until December 2004, 1137 de novo renal transplantations were performed, all from deceased donors. The mean age of the recipients was 48 years (range, 4-66 years); 606 recipients were females (53%) and 531 were males (47%). At the time of the transplantations 188 kidney recipients were CMV seronegative (17% of all recipients). The 125 seronegative kidney recipients, who had received the graft from seropositive donors, were subdivided into three groups according to the CMV prophylactic regimen: 53 patients received hyperimmune gammaglobulin (Cytotect, Biotest); combined prophylaxis (hyperimmune gammaglobulin plus ganciclovir – Cymevene, Roche) was administered to 30 patients and 42 patients received ganciclovir monophylaxis. Twenty-two seronegative patients, who had
undergone transplantations before January 1997 and had not received CMV prophylaxis, served as the control group.

**Methods:**

Determination of CMV-serostatus and acute CMV-infection with serologic method and CMV-antigenemia test was carried out according to the previous paragraph. All patients were monitored for CMV antigenemia and CMV antibodies weekly for 4 months after transplantation during prophylaxis and monthly after cessation of prophylaxis for a total of 12 months post transplant. CMV infection was treated with intravenous ganciclovir 2 x 5mg/ kg body weight/day (adjusted according to renal function as recommended by the manufacturer) until antigenemia test was negative. After CMV seroconversion, prophylaxis was discontinued. The CMV infection was classified into several groups according to Ljungman.

In the study the occurrence of CMV-infection was investigated in two periods: during the administration of the prophylaxis – early posttransplant period (first 4 months) and late period from posttransplant 4 till 12 month. During the first year follow-up of 125 seronegative kidney recipients who had received CMV prophylaxis, renal allograft biopsy was performed when rejection was clinically suspected. The histologic findings were assessed by using the Banff 1997 classification. Rejection episodes were treated initially by high-dose intravenous methylprednisolone, and steroid-resistant rejections were treated by antilymphocyte antibody.

**4. Primary CMV-infection in seronegative kidney recipients, diagnostic methods of the CMV-infection and HLA-typing**

**Patients:**

From January 1999 until December 2006, 1213 renal transplantations were performed from deceased donors; all were first transplantations. Of 1213 kidney recipients, 163 were CMV-seronegative at the time of the transplantation (13% of all recipients). 129 of the CMV-seronegative patients received graft from CMV-seropositive donors. These 129 high-risk patients were investigated in our study.

**Immunosuppressive therapy:** The immunosuppressive regimen included calcineurin inhibitor (cyclosporine, 756 patients or tacrolimus, 457 patients), mycophenolate
mofetil (MMF) and corticosteroid. For high-risk patients in terms of hyperacute or acute rejection (panel reactive antibody level >85%) induction therapy with thymoglobulin was indicated for 10 days.

*CMV prophylaxis:* All 129 seronegative kidney recipients with seropositive donors received CMV-infection prophylaxis with ganciclovir *p.o.* or valganciclovir - the dose was adjusted according to renal function as recommended by the manufacturer.

*CMV monitoring:* Determination of CMV-serostatus and acute CMV-infection with serologic method and CMV-antigenemia test was carried out according to the previous paragraph. All patients were monitored systematically for CMV-antigenemia and CMV-antibodies during the first 12 months.

CMV-infection was treated with intravenous ganciclovir until antigenemia was negative. The CMV infection was classified according to Ljungman. The CMV infection severity was defined as the occurrence of the symptoms and, if occurred, as the above mentioned classification. The CMV end-organ disease was defined as the most severe infection.

*HLA typing:* To determine whether CMV-infection is related to any HLA specificities, the incidence of active CMV-infection and CMV-disease was analysed in relation to HLA-A2, HLA-B12, HLA-Cw7, HLA-DR6, HLA-DR11 and HLA-DQ3 types. HLA-A, -B and -C typing was performed by the standard NIH microlymphocytotoxicity method (NIH). Earlier (before 2006) HLA-DR and -DQ antigens were determined on B-enriched lymphocyte suspensions separated from peripheral blood by the long incubation time cytotoxicity testing and repeated by the DNA technique only in the case of ambiguous result; while now HLA-DR and -DQ antigens were determined by the DNA-based PCR-SSP technique.

HLA typing is routinely performed for the recipients before enrolling on the kidney waiting list and for the donors exactly before the transplantation in order to recognize the HLA matching according to guidelines of the European Federation for Immunogenetics and Eurotransplant.

**Statistical analysis:**

In the studies categorical data were statistically analysed using the chi square test, Fisher’s exact test, and Kruskal-Wallis non-parametric test. *P* values <0.05 were
considered significant. The Mann–Whitney $U$ test was used for comparisons with quantitative variables.

In HLA-type and susceptibility to CMV-infection investigating study cumulative incidence was estimated by the Kaplan–Meier method. A Cox proportional hazards model was used to identify independent predictors of CMV primary infection with these variables: induction therapy, graft rejection and/or treatment for rejection, HLA type, number of HLA-mismatches and age. The patients were homogenous in terms of other influencing factors (CMV serostatus, type of immunosuppression, CMV prophylaxis), so these factors were not taken into account in statistical analysis. Univariate and multivariate Cox regression analysis was performed. All $P$ values were two sided and the appropriate significance level was considered by the Bonferroni correction: values $<0.0083$ ($0.05/6 = 0.0083$) were considered statistically significant. Calculations were made using the StatsDirect computer software program (I. Buchan, Cambridge, UK) and SPSS software program.

**Results**

1. **Results of data analysis of CMV-seroprevalence among donors and elderly**

While investigating the CMV serostatus of the donors and elderly we found that of 2270 1959 (86%) were CMV seropositive (anti-CMV IgG positive) and 311 (14%) were CMV seronegative (anti-CMV IgG negative). In the youngest age-group we found the seroprevalence to be 72%. It means that the Hungarian population acquires the infection in the childhood or in the early adulthood mainly. The seropositivity is growing with the age and is almost 100% in the eldest age group.

The serostatus of the organ-donors was analysed in correlation with gender data. Of 1278 males 1060 were CMV seropositive (83%) and of 792 females 701 (89%) were seropositive. The difference between males’ and females’ CMV seroprevalence was found to be significant ($P=0.0006$), CMV-seropositivity occurred significantly more often among females than among males. In accordance with CMV epidemiology of adults, this difference is probably due to anatomical differences in genitals and habits of sexual behaviour. This hypothesis was proved by the analysis of the seroprevalence data of children (age: 2-15 years), the
difference among boys and girls was not significant (P=0.12) and so the hypothesis considering the sexual differences was right. The investigated group was widely age-distributed and great in number, the age distribution was in accordance with demographic data of Hungarian Central Statistic Institute and so it well represents the Hungarian population. We may conclude that the found high CMV-seroprevalence of 86% represents the prevalence of Hungarian population. Today the opportunity for CMV-seronegative recipients to get a graft from seronegative donor is statistically only 2%. We hope that in the future in case of economic and cultural (health education) development the CMV-seroprevalence in Hungary will decrease and the pool of organs from appropriate donors will grow, and so the danger of the severe primary CMV infection will decrease.

Data concerning connection between CMV-seropositivity and certain blood groups were also investigated. The question was did certain blood groups influence susceptibility to CMV-infection? Data of 1124 donors were investigated. In this study we found no significant difference between CMV seroprevalence of different blood groups (overall P=0.39).

2. Results of comparison of laboratory methods for diagnosis of acute CMV-infection after solid-organ transplantation

1). Results of comparison of serologic method, CMV antigenemia test and "shell vial" virus-isolation

Of 80 investigated transplant patients 17 (21%) had acute CMV-infection, the diagnosis was proved by laboratory method. After it the adequate therapy was started, all patients recovered, except one, his diagnosis and therapy was late and the patient died from severe pneumonia. Proportion of CMV-infection among heart transplant patients was higher (67%) than among others.

CMV antigenemia test showed positivity for 16 infected patients (94%) and in one case it was false-negative. This method detected the infection earlier than the other methods. The antigen positive cells appeared in the same time or earlier than the symptoms developed, number of positive cells was maximal at the time of severe symptoms and decreased during recovering.

The diagnosis of CMV-infection was carried out by the virus-isolation later in contrast to antigenemia test (difference was at least 3 days), and it was positive only
for 1 week (viraemia lasts only for several days). Of 17 infected cases 6 (35%) were false-negative by virus-isolation.

Of 15 cases 6 (40%) were false-negative by serologic procedures. In this cases the CMV specific IgM appeared, if at all, only a few weeks later after the development of CMV-disease.

While screening of the samples of 10 healthy persons, we found no false-positive cases by antigenemia test, we saw aspecific fluorescence in two cases by virus-isolation and we found two ambivalent results of anti-CMV IgM by serologic tests. The sensitivity of antigenemia test was 94%, the specificity was 100%, and the predictive values were 100% and 91%. The sensitivity and negative predictive values of virus-isolation and serologic test were under 65%, it is not acceptable.

2). Results of comparison of CMV antigenemia test and PCR test

CMV antigenemia test was positive in 4 transplant patients of 15, among them three were positive by PCR either. Of these 4 patients three were symptom-free. The number of positive cells were under 5/100 000 PBL and the number of DNA copies were under 500/ml in symptom-free cases. These results weren’t considered to be significant. Only one patient had characteristic symptoms of CMV-infection, antigenemia test and PCR test became positive on the 59 post-transplant day (268/100 000 PBL), after initialization of therapy the patient recovered on day 21 and the antigenemia test became negative. PCR test’ positivity lasted for 32 days. The infection developed between two control days (54. and 91.) of the designed follow-up.

The sensitivity and specificity of both methods were highly acceptable (>75%), the values were almost equal. The question that which one was more useful in the diagnostics was answered by checking of the methods’ applicability and the local opportunities.

We have found a few disadvantages of PCR test:
- while compared the expenses of the tests, the price of PCR test was found to be 10 times higher than of antigenemia test
- we couldn’t determine exactly the cut-off value of the PCR test (which DNA copies number indicates the administration of medicine), and there are no
unambiguous directives for cut-off value in the literature. Probably it is better to pay attention to the changes in the copies number and not to absolute values. The use of the antigenemia test was much more less labor-intensive in our practice. The disadvantage of the antigenemia test is the subjectivity of the results; the reading of the results requires experience.

3. Results of the comparison of CMV-infection preventing prophylactic protocols in high-risk kidney transplant patients

**CMV-infection in the first four post-transplant months during the administration of the prophylactic therapy:**

In group I, of 53 seronegative renal transplant patients (R-/D+) who had received hyperimmune gammaglobulin for prophylaxis 31 (59%) developed CMV-infection. Nine patients experienced asymptomatic and 22 had symptomatic infection (median week: 7.7th, range: 6-10).

In group II, of 30 patients who had received combined prophylaxis seven (23%) developed CMV-infection (median week: 8.7th, range: 8-10), three were symptom free, and four were symptomatic.

In group III, of 42 patients who had received ganciclovir monoprophylaxis nine (21%) developed CMV-infection (median week: 8.6th, range: 7-10), six were asymptomatic, and in three cases a CMV-syndrome developed.

In the group IV (control) without CMV prophylaxis, all 22 recipients developed CMV-infection (100%) (median week: 6.6th, range: 5-7), four developed CMV-syndrome, 10 developed CMV end-organ disease, and one patient died from CMV-pneumonia. All patients seroconverted.

There was significant difference in CMV-infection occurrence between the treated groups and the control group (overall P<0.0001, individual comparisons P<0.0001).

In the groups with prophylaxis (groups I-III), CMV-infection occurred, if at all, in average 2 weeks later than in patients without prophylaxis (8.3 versus 6.6 weeks).

While comparing the prophylactic groups we found that the infection occurred more often in the group I (P=0.0027 and 0.00035) and in average 1 week earlier than in other two groups. There was no significant difference in the incidence of the infections in groups II and III.

**CMV-infection after prophylaxis cessation, months 5-12**
In group I, of 53 patients 10 (19%) developed CMV-infection in the period from 4 till 10 months with mild symptoms, and 12 had not got infection at all in the first posttransplant 12 months.

In group II, of 30 patients 2 (7%) developed primary infection in the 10th month with mild symptoms, and 21 patients remained CMV-free in the first 12 months.

In group III, of 42 recipients 4 (10%) developed CMV-infection in the period from 5 till 10 months, 2 cases were asymptomatic and 2 were with mild symptoms, 29 patients (69%) from this group remained CMV-free till the end of the study (12 months).

Of the total 125 recipients with prophylaxis 63 (50%) developed CMV-infection up to 12 months post transplant, seroconversion didn’t follow the infection in 9 cases (14%). Of 63 infections 16 (25.4%) developed after the cessation of the prophylaxis in the period from 5 till 10 months (late-onset infection).

**CMV-infection and graft-rejection**

Of all 147 seronegative recipients (R−/D+) 43 developed acute graft-rejection. 25 had both biopsy-confirmed acute rejection and CMV-infection in the first posttransplant year. Of total 85 CMV-infections 20 developed after acute rejection (24%); time from diagnosis of rejection to CMV-infection was 45 (22–112) days. Of total 43 episodes of acute rejection only 5 (12%) developed after CMV-infection: time from CMV-infection to rejection was 50 (40–70) days.

**4. Results from the analysis of the possible association between susceptibility to CMV-infection and certain HLA-types**

**Demographic characteristics and CMV infection**

Of the all investigated 1213 kidney transplanted patients, 630 were females (52%) and 583 were males (48%); the mean age at the time of transplantation was 47.3 years (range 3–72 years). Of 163 CMV-seronegative recipients 54 (33%) were females and 109 (67%) were males; the mean age was 37.6 years. The mean age of 34 CMV-seronegative recipients with seronegative donors (R−/D−) is lower: 33.5 years (range: 3–57).

Although the difference in the gender proportion is negligible among all 1213 recipients (48% and 52%), the difference in this proportion among CMV-seronegative patients is highly significant (33% and 67%, P <0.001). We have
expected more seronegative females than males since the mean age of females (35.6 years) was lower than that of males (41.5 years) in this group and it is well known that the CMV seroprevalence is growing with age. The number of females among seronegative recipients was much lower than of males. This fact confirms the results of CMV-seroprevalence study. The mean age of CMV-seronegative recipients was lower than that of all 1213 transplant patients (37.6 versus 47.3 years); the difference is highly significant ($P < 0.0001$).

**Incidence of CMV infection**

Of 129 CMV-seronegative recipients with seropositive donors 49 (38%) developed acute primary CMV-infection during the first post-transplant year (average period: 101.6 days posttransplant). Among 34 seronegative patients who had received the graft from seronegative donors, only one developed CMV infection with mild symptoms on day 124 posttransplant.

The occurrence of CMV-infection in patients with HLA-A2, HLA-DR6, HLA-DR11 was higher, while the occurrence in those with HLA-B12 and HLA-Cw7 was lower than that in patients negative for these HLA types, but the differences were not significant. However, a significant difference was found in the HLA-DQ3 positive group versus HLA-DQ3 negative patients: of 68 DQ3 positive patients 32 and of 61 DQ3 negative patients 17 had CMV primary infection ($P = 0.002$) in univariate analysis. The infections occurred 2 weeks earlier in average in the HLA-DQ3 careers: 78.7 posttransplant days versus 96.9 days. To determine whether these results were influenced by other risk factors, we performed the multivariate Cox regression analysis that showed that the HLA-DQ3 positivity is an independent predictor of CMV acute infection in R−/D+ recipients.

**Severity of CMV infection**

Of 68 HLA-DQ3+ patients, 32 developed primary CMV-infection (47%), 8 of them were CMV end-organ diseases, 16 CMV syndromes [24 symptomatic infections (75%)] and 8 were asymptomatic infections. Of 61 HLA-DQ3− patients 17 (28%) developed CMV-infection: only 1 had CMV end-organ disease, 8 had CMV syndromes [9 symptomatic infections (53%)] and 8 infections were asymptomatic. The severity of CMV infection was higher in HLA-DQ3 careers.
Conclusions

1. Conclusions from data analysis of CMV-seroprevalence among donors and elderly

1). In the study it was determined that the CMV-seroprevalence of Hungarian population is high: 86%. The seroprevalence of the youngest age group (2-20 years) was 72% and so it was concluded that Hungarian population acquires the infection in the childhood or in the early adulthood mainly.

2). For the first time it was found and proved that the female sex is a risk factor for CMV-infection. CMV-seropositivity in the adults occurred significantly more often among females than among males. This fact must be taken into consideration during the planning of patients’ follow-up and therapy.

3). The reasons of sexual differences in CMV-seroprevalence are due to the beginning of the sexual life and probably relate with anatomical differences in genitals and habits of sexual behaviour.

2. Conclusions of comparison of laboratory methods for diagnosis of acute CMV-infection after solid-organ transplantation

1). For the first time in Hungary the CMV antigenemia test was introduced by our laboratory for the acute CMV-infection of transplanted patients. In the comparing study it was proved that the highly sensitive and specific CMV antigenemia test is more advantageous than the conservative methods for this purpose.

2). The cut-off value of CMV antigenemia test was determined as 5 positive cells/100 000 PBL, the value depends on the clinical status of the patient. With the modernization and with automatization of the method the time of the test was shortened from 6 to 4 hours.

3). The results of the comparing study proved that CMV antigenemia test and PCR test as quantitative methods with high sensitivity and specificity are well suitable for CMV-infection detection in transplant patients. Considering the advantages and disadvantages of CMV antigenemia test and PCR, we recommend the use of cheaper and less labor-intensive antigenemia test for kidney transplant patients under the Hungarian circumstances.
4). The algorithm of diagnostic procedures for acute CMV-infection of immunocompromised was worked out and published in the “Directives for Infectologists”.

5). We suggest to arrange the control laboratory measurements for CMV infection once in a week or two weeks in case of pre-emptive therapy of patients with high risk factors during first posttransplant 3-6 months.

3. Conclusions of the study comparing the effectiveness of different prophylactic protocols preventing CMV-infection in high risk kidney transplanted patients

1). The study proved that CMV-infection prophylaxis is essential for high risk patients in the early posttransplant period of 3 months, the administration of any of investigated prophylactic protocols is advantageous in comparing with prophylaxis-free management of those patients.

2). The study proved that monoprophylaxis with ganciclovir or valganciclovir is the most effective and cost-effective procedure as compared to other protocols.

3). So far as there is a failure to develop humoral immunity after the primary CMV-infection, the patient remains in the high risk group henceforward and requires follow-up.

4. Conclusions of the analysis of the correlation between susceptibility to CMV-infection and certain HLA-types, the role of the genetic predisposition

1). For the first time it was proved and published that the HLA-DQ3 positivity is a risk factor for susceptibility to CMV-infection. The multivariate Cox regression analysis showed that the HLA-DQ3 positivity is an independent predictor of primary CMV-infection in CMV seronegative recipients with seropositive donor grafts. The cognition of HLA-DQ3 is useful in the prediction of acute CMV infection in high-risk patients.

2). Our report concerning genetic predisposition provides the clinical human basis for further genomic analyses of susceptibility to certain infections.
List of publications

**In connection with theme**


   **IF: 1.830**

   **IF: 3.167**


   **IF: 1.923**

**IF:** 1.204


**Independent publications**


**IF: 0.799**


**IF: 4.035**


Bookchapters in connection with theme
