The article discusses the problem of cytomegaloviral persistence asymptomatic course among young patients with community-acquired pneumonia and in healthy population group based on specific immunoglobulins M and G appearance in blood and antibody avidity value (the duration of persistent). The connection between viral persistence and prognosis of community-acquired pneumonia (by pneumonia severity index in PORT) is also recognized.

**Aim** of the scientific work is to study the prevalence of cytomegaloviral persistence among young patients with community-acquired pneumonia for optimization the plan of clinical examination and prognosis for this patient category.

**Materials and methods.** One hundred and five patients with community-acquired pneumonia and 61 healthy individuals (aged from 18 to 44 years) were examined for cytomegaloviral biomarkers (CMV IgG, CMV IgG avidity) and by PORT-scale. Positive result for viral persistence was compared with gender, age subtypes and pneumonia severity index in both groups.

**Results.** Cytomegaloviral persistence prevalence rate among patients with community-acquired pneumonia was 48.2% versus 20.5% among healthy individuals (P = 0.003). The patients with community-acquired pneumonia had higher CMV IgG avidity value (P = 0.007), it was more common for female patients (P = 0.043; $\chi^2 = 8.164$). The cytomegaloviral persistence prevalence increased with age (P = 0.045) and correlated with pneumonia severity index according to PORT-scale (P < 0.0001).

**Conclusions.** The patients with community-acquired pneumonia differ in significantly higher cytomegaloviral prevalence rate (P = 0.003) from the healthy respondents. This rate increases with age, negatively impacts the pneumonia prognosis (by PORT-score). The duration of cytomegaloviral persistence (based on the CMV IgG avidity value recognition) does not depend on age in both comparison groups (P > 0.05).
Цель работы — исследовать распространенность цитомегаловирусной персистенции у молодого контингента пациентов с негоспитальной пневмонией для последующей оптимизации схемы обследования и прогноза таких больных.

Материалы и методы. У пациентов молодого возраста (18–44 лет) с установленным диагнозом негоспитальной пневмонии и практически здоровых респондентов изучали показатель распространенности цитомегаловирусной персистенции путем установления маркеров CMV IgG, CMV IgG (авидность) в крови, исследовали связь персистенции с половыми и возрастными особенностями, а также риском летальных исходов по шкале PORT в основной группе.

Результаты. Показатель распространенности цитомегаловирусной персистенции оказался статистически более высоким в группе больных негоспитальной пневмонией и составил 48,2 %, в группе здоровых — 20,5 % (р = 0.003). Пациенты основной группы характеризовались более высокими значениями CMV IgG авидности (р = 0,007), что наиболее выражено у женщин с негоспитальной пневмонией, чем у мужчин (р = 0.043; χ² = 8.164). Показатель цитомегаловирусной распространенности растет соответственно возрасту пациентов (р = 0.045) и коррелирует с классом риска летальных исходов по шкале PORT (р < 0.0001).

Вывody. Пациенты с негоспитальной пневмонией отличаются от здоровых респондентов популяции более высоким показателем распространенности цитомегаловирусной персистенции, который увеличивается с возрастом, негативно влияет на прогноз для данной когорты пациентов в виде ассоциации с классом риска летальных исходов (по шкале PORT). Продолжительность цитомегаловирусной персистенции (по уровню авидности антител) не зависит от возраста в обеих группах (р > 0.05).

Background

The role of cytomegaloviral infection (CMVI) in immuno-suppressive conditions complications remains great clinical problem in modern infectology, gynecology, pediatrics and immunology. However, every branch of medicine develops own unique guidelines to solve severe pathological effects of CMVI. After a primary infection, human CMVI remains latent in certain human cells. Different stimuli, including immune deficiency and severe infection, can trigger the reactivation of latent CMVI. In the last decade, the role of the reactivation in immunocompetent patients with serious illness has been intensively studied; however, the knowledge of the potential role of moderately severe infections on CMVI dynamics is limited [11]. For a long time CMVI has been recognized as one of the most important pathogens in immunocompromised patients, such as solid organ transplant recipients [1,13], patients with haematological malignancies [2], and HIV patients [6]. In the last decade the role of serious infections in activation of latent CMV infection in immunocompetent patients has also been scrutinized [10].

At the same time, scientific progress in the diagnosis of community-acquired pneumonia (CAP) and the development of highly effective antibacterial drugs for its treatment do not provide a full positive effect, which can be explained by the conditions of CAP occurrence transformation, changes in the virulence of pathogens and the immune reactivity of the patient’s body [9,12]. The 35–60 % of etiologically determined CAP is S. Pneumoniae. Viral etiology of CAP is extremely controversial. 10–30 % of patients do not expectorate sputum, 15–30 % take antibiotics until a specific laboratory examination. In 30–65 % the data of microbiological / virological examination is questionable [7].

These facts suggest the probable possibility of avoiding the protective immune attack by some kind of latent persistent pathogen, which affects immunity, without specific clinical features, that results in superinfection and makes hidden conditions for bacterial comorbidities like CAP. The CMVI prevalence among young CAP patients has not been studied yet, though its knowledge can optimize specific etiological and immunological diagnostics and correct treatment.
CMV IgG avidity, CMV reconvalescent; >60 % – high avidity, anamnestic CMV-antibodies.

Statistical processing of results was performed by SPSS 12.0 for Windows (Grand Pack, Serial Number 9593869). Previously, the verification of variables values on the normality of distribution by the Kolmogorov-Smirnov method was carried out. For the normality of variables determination for Poisson distribution with insignificant probability of error (P > 0.05), parametric tests were used for further statistical analysis (Student’s t-test for two dependent or independent variables (sampling), a simple analysis of variance (ANOVA)) was used for more than 2 independent variables and a simple dispersion analysis with repeated measurements was used for more than 2 dependent variables (samples). Non-parametric tests (U-Mann–Whitney test for 2 independent variables (samples), Wilcoxon test for two dependent variables (samples) comparison, Kruskal–Wallis H test for more than 2 independent variables (samples) comparison and the Friedman test to compare more than two dependent variables (selections) that allow one to examine the effect of one or more independent variables on dependent variable were used in case of non-normal distribution of variables.

Descriptive methods were compiled by constructing cross-tables, statistics for χ² for the nominal scale, comparing two independent samples (Student’s T-criterion), one-way ANOVA one-dimensional analysis (Fisher’s F-criterion), Scheffe’s and Duncan’s posteriori test for comparison of average values. Spearman rank correlation was used for associative connections revealing between score characteristics and clinical features of CAP, which belonged to the interval scale, in connection with the non-compliance of the mentioned indices with normal distribution. The investigated values are represented as “average ± standard error of average value” (M ± m) or “average ± standard deviation” (M ± σ). The results of comparisons were considered to be significant when the probability of error (p) was not more than 0.05.

Results and discussion

The CMV prevalence (according to CMV IgG appearance) among CAP patients was revealed significantly higher than in the control group (P = 0.003). The results are shown in Table 1.

The average titer of CMV IgG among CAP patients was (8.86 ± 0.70) and ranged from 0.0 to 39.1, while in the group of healthy individuals the average titer of CMV IgG was (5.26 ± 0.70) and ranged from 0.0 to 18.3 (the difference was insignificant, t = 1.581, P = 0.701). The average titer of CMV IgG was (6.29 ± 0.70) and ranged from 0 to 39 among all respondents (166 observations). Thus, there was a tendency toward an increasing in the absolute value of the average titer of CMV IgG in the group of CAP patients in comparison with the control group.

Classification of all respondents according CMV IgG avidity showed in both groups of comparison that CMV-positive respondents in the majority of cases had high CMV IgG avidity, indicating rather a long CMV persistence in these respondents. It is also noteworthy that the percentage of different values avidity among patients with CAP was higher than among practically healthy persons (P = 0.007): 48.6 % vs 45.9 % (high avidity), 21.9 % vs 8.2 % (intermediate avidity) and 6.7 % vs 1.6 % (low avidity) (Table 2).

Gender characteristics of the classified respondents in both comparison groups revealed that among CAP patients male significantly differed from women (P = 0.043; χ² = 8.164); intermediate CMV IgG avidity value was 15.2 % among males (16 persons) versus 6.7 % (7 persons) among females, high CMV IgG avidity was detected in 18 men (17.1 %) and 33 women (31.4 %). A similar analysis in the control group did not reveal significant difference according to gender (χ² = 2.244; P = 0.523).

Analysis of CMV prevalence (by CMV IgG appearance) according to age found significantly increased number of CMV-positive individuals among elderly CAP patients (P = 0.045): 1.0 % – in category of 20–29 years old, 3.8 % – in category of 30–39 years old, 16.2 % – in category of 40–44 years old. Analysis of CMV prevalence (by CMV IgG avidity) according to age did not find significant differences neither among CAP patients (χ² = 11.402; P = 0.249) nor among healthy persons (χ² = 4.793; P = 0.852).

We also tried to reveal the dependence of CAP progression on CMV IgG avidity. Results are given in Table 3.

The proportion calculation among patients with CAP according to its severity and the value of CMV IgG avidity was performed in CMV-positive respondents of the main group (80 persons). CMV-positive CAP patients with high CMV IgG avidity differed in CAP severity (P < 0.0001): PORT I was defined in 5 (6.3 %) persons, PORT II – in 22 (27.5 %) patients, PORT III – in 17 (21.3 %) persons. A similar feature was found among CMV-positive patients with low CMV IgG avidity: patients with PORT I were not found, PORT II and III were diagnosed in 3 patients (3.7 %) in each group, PORT IV was detected in 7 % (1 patient). Thus, we have found a direct relationship between CAP progressive severity and CMV duration.

Our clinical research shows significantly high level of undiagnosed persistent CMV incidence among young individuals. Official data of CMV prevalence speaks about 30 % of world population under 30 years of age with positive CMV IgG [11]. We enrolled the individuals 18–44 years old (young category) in the study. The different CMV-indexes in our work (48.2 % among CAP patients and 20.5 % among healthy individuals) may be associated with immune response peculiarities, therefore only respondents without comorbidities were included in the study. That is why CMV prevalence can lead to some immune system dysfunction, which influences the severity of pneumonia course.

The fact of significantly higher CMV IgG content in CAP patients than among healthy ones may explain the susceptibility of CMV-positive individuals to different bacterial associations (including CAP).

The persistence avidity index among all respondents is responsible for CMV duration: the high avidity value is a result of long-term viral persistence [2,8,10]. The higher CMV IgG avidity among CAP patients confirms already known data and shows that CMV persistence increases the risk of additional bacterial comorbidities.

The gender difference according to CMV presence needs additional study. The longer CMV duration among females versus males can be the result of transmission features and may deal with hormonal differences, which have not been investigated yet.
Table 1. The cytomegaloviral prevalence among patients with community-acquired pneumonia and healthy individuals

<table>
<thead>
<tr>
<th>CMVI persistence</th>
<th>CAP patients (n = 105)</th>
<th>Healthy individuals (n = 61)</th>
<th>χ²</th>
<th>r (Spearman’s)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG CMV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– positive</td>
<td>80</td>
<td>34</td>
<td>8.685</td>
<td>-0.228</td>
<td>0.003</td>
</tr>
<tr>
<td>– doubtful</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>– negative</td>
<td>24</td>
<td>27</td>
<td>16.3</td>
<td>0.155</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 2. Classification of patients with community-acquired pneumonia and healthy individuals according to CMV IgG avidity

<table>
<thead>
<tr>
<th>Value of CMV IgG avidity</th>
<th>CAP patients (n = 105)</th>
<th>Healthy individuals (n = 61)</th>
<th>χ²</th>
<th>r (Spearman’s)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low – primary infection (1–39 %)</td>
<td>7</td>
<td>6.7</td>
<td>1</td>
<td>1.6</td>
<td>12.134</td>
</tr>
<tr>
<td>Intermediate –reconvalescence (40–60 %)</td>
<td>23</td>
<td>21.9</td>
<td>5</td>
<td>8.2</td>
<td>13.333</td>
</tr>
<tr>
<td>High – anamnestic antibodies (&gt;60 %)</td>
<td>51</td>
<td>48.6</td>
<td>28</td>
<td>45.9</td>
<td>15.385</td>
</tr>
</tbody>
</table>

Table 3. Dependence of community-acquired pneumonia prognosis (according to PORT-scale) on CMV IgG avidity

<table>
<thead>
<tr>
<th>Value of CMV IgG avidity</th>
<th>PSI</th>
<th>Total (n = 80)</th>
<th>χ²</th>
<th>r (Spearman’s)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (1–39 %)</td>
<td>–</td>
<td>–</td>
<td>31.446</td>
<td>0.305</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intermediate (40–60 %)</td>
<td>–</td>
<td>–</td>
<td>13.333</td>
<td>-0.099</td>
<td>0.007</td>
</tr>
<tr>
<td>High (&gt;60 %)</td>
<td>5</td>
<td>6.3</td>
<td>15.385</td>
<td>-0.141</td>
<td>0.007</td>
</tr>
</tbody>
</table>

There is an increasing tendency of CMVI persistence with age [8], which is confirmed by our results. So the risk of latent CMVI appearance increases with age and all supposed immunological dysfunctions depend on contributing individual and environmental factors for its clinical manifestation (CAP is among them).

The clinical relevance of our study was based on comparison of CAP severity and CMVI duration. The obtained results give a clear picture of direct dependence: the growth of PSI is accompanied by CMV IgG avidity increase. Such dependence goes to prove that long-term CMVI persistence complicates the course of CAP through certain pathogenetic mechanisms.

Conclusions

1. CAP patients differ from healthy individuals by higher incidence of CMVI persistence, which leads to CMV IgG level elevation in blood samples. The value of CMVI persistence among young patients with CAP ranges 48.2 % versus 20.5 % of control healthy ones (P = 0.003).
2. CAP respondents have a tendency toward an increase in the average titer of CMV IgG absolute value. According to all values of CMV IgG avidity CAP patients are characterized by longer viral persistence period than control group respondents (P = 0.007), which is particularly in evidence (P = 0.043; χ² = 8.164) among CAP females.
3. CMVI prevalence among CAP patients has an increasingly positive association with the age (P = 0.045) and depends on PSI (P < 0.0001).

Prospects for further research. The obtained results will have a continuation on the look-out for pathological mechanisms of CMVI influence on immunological, genetic, hormonal links among young individuals in order to prevent bacterial comorbidities (CAP as well). New discoveries in this area will allow optimizing the clinical, diagnostic and therapeutic approach, predicting the course of CAP and preventive measures developing.

Conflicts of Interest: author has no conflict of interest to declare.

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