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ASSESSMENT OF THE CLINICAL COURSE OF COMMUNITY ACQUIRED PNEUMONIA IN YOUNG PATIENTS, TAKING INTO ACCOUNT THE CMV-PERSISTENCE AND ITS SEVERITY

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Abstract

Today, the question of establishing the features of clinical course of community acquired pneumonia (CAP) due to the presence or absence of CMVI-infection persistence in the human body, the study of the type and nature of the effects of concomitant persistent CMVI on the symptoms of CAP, the effectiveness of treatment, was one of the unexplored. This issue is particularly relevant for young people, as it does not only damage the condition of patients but also directly and indirectly affects the economic component of the disease, increasing direct and indirect losses for the able-bodied patient and the state as a whole.

Key words: community acquired pneumonia; cytomegalovirus infection; clinical course; young age; PORT.

Background

Cytomegalovirus infection (CMVI) is a widespread disease of viral etiology. According to WHO, the proportion of seropositives among the adult population of Ukraine is 75-98% [1], and the WHO Regional Office of Europe includes CMVI in the list of diseases that determine the future of infectious pathology [2]. A glance at CMVI in the context of

opportunistic disease indicates its clinically significant course, against the background of existing immunological changes. However, in recent years, scientists have begun to note that the persistent form of CMVI can affect immune status, thus contributing to the attachment of other infectious pathologies and their more severe course [5].

When studying the peculiarities of the effect of CMV on the respiratory organs, Dzublik Y.A. et al. [3-4] concluded that virological examination of immunocompetent patients with community acquired pneumonia (CAP) was due to the fact that such a severe course of CAP was provoked in 20% cases by CMVI persistence. Ivanova L.A., interested in the examination of often respiratory diseases of children of primary school age, in their works concluded that 40% of persons of this age category at the stage of primary examination were not diagnosed with persistent herpetic infection (10%), which probably had an effect on cellular immunity and contributed to frequent respiratory infections [6]. In addition to sputum shedding, radiographs of the lungs, and general clinical methods of diagnosis regulated by current guidelines, many authors emphasize the accompanying immunological changes that occur in the CAP and can be a primary problem, that is, serve as a basis for attachment of bacterial fluoridation [9], and to deepen again on the background of the existing CAP.

That is why studying the clinical course of CAP in young patients, taking into account CMVI-persistence is an urgent, timely issue of modern infectology.

Aim: To investigate the peculiarities of clinical course of CAP in young patients, taking into account CMVI-persistence.

Materials and methods

According to the aim and the task of the study, 105 patients with CAP (51 [48.6%] men and 54 [51.4%] women) who were hospitalized at the pulmonology department of the city clinical hospital № 1 in Vinnytsia were examined during 2015-2017. 61 (26 [42.6%] males and 35 [57.4%] females) were considered healthy.

To assess the clinical course of CAP, we used the standard diagnostic approach outlined in the Ministry of Health of Ukraine Orders No. 128 (2007) [7] and the state clinical guideline “Community acquired and hospital (nosocomial) pneumonia in adults: etiology, pathogenesis, classification, diagnostics, antibiotic therapy, 2014” governing a comprehensive clinical approach to the diagnosis, clinical classification and treatment of CAP. The results of the analysis of clinical and functional signs of lung damage were taken into account, assessing the severity of clinical symptoms of the disease in points (cough, its character (productive, unproductive) and expressiveness (severity) - in points of analog scale from 0 to 3, nature of

sputum, respiratory rate in points on the MRC (Medical Research Scale) - 0 to 5) and objective symptoms (physical and laboratory). According to the existing requirements and for more objective stratification of patients by severity we used the point evaluation of risk factors of lethal consequence according to the results of the study Pneumonia Patient Outcomes Researches Team (PORT).

All CAP patients were examined in the hospital for the first three days after admission to the hospital. The severity of the clinical course of CAP in patients should also be evaluated, taking into account the area of lung tissue lesion, its localization and features (including the presence of concomitant dry or exudative pleurisy and lung destruction) were established clinically, verification was performed by X-ray examination. In addition, the nature of the likely secondary lesion of the cardiovascular and other systems due to CAP was evaluated.

The presence of CMVI was determined by identification of class G antibodies to cytomegalovirus. The CMVI prescription was evaluated by the avidity level of anamnestic antibodies.

Statistical processing of the results was performed on a personal computer using the SPSS 12.0 statistical software package for Windows, Grand Pack, Serial Number 9593869). Descriptive statistics were performed by constructing cross-tables, χ^2 statistics for the nominal scale, comparison of two independent samples (Student's T-test), one-way ANOVA (Fisher's F-test), a posteriori Sheff average comparison test, Duncan. The values studied are presented as “mean ± standard error of mean” (M ± m) or “mean ± standard deviation” (M ± σ). The results of the comparisons were considered valid when the probability of error (P) was not more than 0.05 [8].

Results

We analyzed the distribution of patients with CAP, depending on the severity and degree of persistence of CMVI, on the one hand, and depending on the severity of the course of CAP according to the PORT scale, on the other (Table 1).

As the number of patients with risk class IV was 9, we subsequently combined them with a group of patients with risk class III.

Table 1 - Frequency analysis of distribution of patients of young age by severity of CAP according to the PORT scale depending on the degree of persistence of CMVI and the avidity level of CMV antibodies

Index	CAP severity according PORT			Total (n=105)	χ^2 / p
	I class risk (n=19)	II class risk (n=46)	III-IV class risk (n=40)		
CAP patients without CMVI persistence (n)	13	8	3	24	28,500 / <0,0001
% (CAP severity / CMVI persistence)	68,4/54,2	17,4/33,3	7,5/12,5	22,9/100,0	
CAP patients with CMVI persistence (n)	6	38	37	81	
% (CAP severity / CMVI persistence)	31,6/7,4	82,6/46,9	92,5/45,7	77,1/100,0	
CAP patients with mild CMVI persistence (n)	3	21	15	39	33,404 / <0,0001
% (CAP severity / CMVI persistence)	15,8/7,7	45,7/53,8	37,5/38,5	37,1/100,0	
CAP patients with moderate CMVI persistence (n)	3	14	14	31	
% (CAP severity / CMVI persistence)	15,8/9,7	30,4/45,2	35,0/45,2	29,5/100,0	
CAP patients with severe CMVI persistence (n)	-	4	8	12	
% (CAP severity / CMVI persistence)	-	8,7/33,3	20,0/66,7	11,4/100,0	
CAP patients with low CMV-avidity (n)	-	3	4	7	30,897 / <0,0001
% (CAP severity / CMVI persistence)	-	6,5/42,9	10,0/57,1	6,7/100,0	
CAP patients with moderate CMV-avidity (n)	-	13	10	23	
% (CAP severity / CMVI persistence)	-	28,3/56,5	25,0/43,5	21,9/100,0	
CAP patients with high CMV-avidity (n)	6	22	23	51	
% (CAP severity / CMVI persistence)	31,6/11,8	47,8/43,1	57,5/45,1	48,6/100,0	

The results show a statistically significant ($p < 0.0001$) increase in the number of patients with CAP in accordance with the appearance of specific CMV antibodies. Thus, 3 patients (7.5% of the total number of patients with III-IV risk classes and 12.5% among patients without verified persistence) were observed among patients with III-IV risk classes of CAP without detectable viral persistence, persistence increases to 15 (37.5% of the total

number of patients and 38.5% among patients with mild persistence). At the same time, there is an increase in the severity of pneumonia from grade I to grade IV on the PORT scale among patients with different levels of persistence ($\chi^2 = 33.404$; $p < 0.0001$). As we can see, in the group of patients with the first class of severity of CAP at a moderate level of CMV-persistence, 3 patients were identified (15.8% of the total number of patients with the second risk class, 9.7% among the patients with moderate persistence), while 14 patients have III-IV severity classes of CAP (35.0% among patients with III-IV severity classes and 45.2% among respondents with an average level of anamnestic antibodies to CMV). During assessing the quantitative ratio of patients with CAP according to the definition of the class of lethal consequences on the PORT scale and the degree of avidity of CMV antibodies, we found an increase in the number of degrees of CMV avidity, and therefore, with the prescription of CMVI-persistence. Thus, the number of patients with III-IV risk classes who had a high degree of CMV-avidity, was 23 (57.5% among patients with III-IV severity and 45.1% among respondents with high avidity), and the number of 6 patients were at risk class 1 (31.6% among patients with grade III-IV severity and 11.8% among high-avidity respondents) ($\chi^2 = 30.897$; $p < 0.0001$). The results obtained during the study probably indicate a special place for CMVI-persistence in the prognosis of the course of CAP and indicate its undeniable influence on the severity of CAP in such patients.

Taking into account the standardized approach to diagnostics of severity of the course of CAP, which is regulated in the Order of the Ministry of Health of Ukraine № 128 of 19.03.2007, the study of the clinical course of CAP in persons with presence and expressiveness of CMVI-persistence was conducted. At the same time, the criteria for comparison were the patient complaints, clinical symptoms of CAP and their severity, objective and laboratory-instrumental examination data, which illustrate the nature and severity of the course of CAP, which were identified during the anamnesis collection. For preliminary assessment of the severity of the course of CAP, we conducted a frequency analysis of the distribution of patients according to clinical signs of the severity of the course (cough, shortness of breath, the nature of sputum, the presence of inflammatory signs in laboratory examinations), depending on the severity of IgG CMV, which allows us to comprehensively evaluate the nature of the influence of CMVI the course and consequences of the CAP. Frequency analysis of the distribution of patients depending on the level of the integrative index of CMVI-persistence is given in table. 2.

Table 2 - Frequency analysis of the distribution of CAP patients by clinical course, depending on the severity level of CMVI-persistence

Index (n, %)	CMVI persistence				p
	CMVI absence (n=23)	Mild (n=39)	Moderate (n=31)	High (n=12)	
Severe chest pain	4 (3,8%)	26 (24,8%)	22 (21,0%)	8 (7,6%)	<0,0001
Severe cough (≥2 points)	9 (8,6%)	26 (24,8%)	27 (25,7%)	8 (7,6%)	0,015
Purulent sputum	3 (2,85%)	13 (12,4%)	4 (3,8%)	1 (0,95%)	0,005
Significant shortness of breath ((≥2 points)	10 (9,5%)	28 (26,7%)	20 (19,0%)	8 (7,6%)	0,012
Sat O_2	5 (4,8%)	14 (13,3%)	16 (15,2%)	6 (5,7%)	0,040
Cyanosis	1 (0,95%)	8 (7,6%)	13 (12,4%)	3 (2,9%)	0,039
38°C hyperthermia and more	3 (2,9%)	13 (12,4%)	9 (8,6%)	6 (5,7%)	0,028
Disorders of consciousness	4 (3,8%)	17 (17,9%)	15 (14,3%)	5 (4,8%)	0,326
Lymphadenopathy	5 (4,8%)	25 (23,8%)	27 (25,7%)	8 (7,6%)	<0,0001
Pleurisy	-	4 (3,8%)	2 (1,9%)	1 (0,95%)	0,474
Violation of liver enzymes	4 (3,8%)	9 (8,6%)	6 (5,7%)	6 (5,7%)	0,144
Disorders of renal indexes	1 (0,95%)	3 (2,9%)	2 (1,9%)	3 (2,9%)	0,181
Anemia	7 (6,7%)	13 (12,4%)	18 (17,1%)	8 (7,6%)	0,119
Leukocytosis	12 (11,4%)	12 (11,4%)	18 (17,1%)	5 (4,8%)	0,320
Lymphopenia	5 (4,8%)	12 (11,4%)	2 (2,9%)	2 (2,9%)	0,166
Shift left	11 (10,5%)	22 (21,0%)	14 (13,3%)	7 (6,7%)	0,747
ESR increased	16 (15,2%)	25 (23,8%)	19 (18,1%)	9 (8,6%)	0,819

When reviewing the results of the frequency analysis of the distribution of patients with CAP according to the presence and degree of severity of CMVI-persistence and clinical symptoms, we have: as the level of IgG CMV increases, the percentage of patients with clinically expressed cough (27 [25.7%] of people at p = 0,015 among patients with moderate viral persistence against 9 [8.6%] patients without verified persistence and 26 [24.8%] patients with mild persistence), purulent sputum (13 [12.4%] at p = 0.005 in subjects with mild persistence against 3 [2.9%] individuals without IgG CMV), high hyperthermia (9 [8.6%] patients with moderate CMV persistence at p = 0.028 vs 3 (2.9%) patients without persistence), expressed chest pain (at p <0.0001 vs patients with moderate persistence) was 26 {24.8%], while in patients without specific CMV antibodies - 4 [3.8%]). A similar pattern is also observed in the analysis of parameters of shortness of breath (p = 0.012), cyanosis (p = 0.039), the percentage value of oxygen saturation (p = 0.040), the severity of lymphadenopathy (p <0.0001), and the increase in the proportion of these patients

corresponds to an increase in CMV-persistence on the level of specific antibodies available. Significant differences in the percentages of the number of patients with clinically significant disorders of consciousness (p = 0.326), pleurisy (p = 0.474) were not detected. When evaluating the data, taking into account the results of the laboratory examination, we see that the dynamics of indicators of renal samples, leukocytes, lymphocytes, hemoglobin, impaired liver and kidney function in the direction of decrease according to the increase in the degree of persistence is characteristic, although not significantly confirmed (p> 0,05).

The table 3 shows the mean values of clinical course of CAP depending on Ig G CMV verification. As is known, the detection of CMV IgG is evidence of persistent CMV. Therefore, according to the availability of this indicator, we divided the patients into the main group and followed the mean values of the main CAP indicators.

Table 3 - Average values of clinical course of CAP according to Ig G CMV verification

Index (M±m)	Ig G CMV		p
	Positive (81 CAP patients)	Negative (24 CAP patients)	
Respiratory rate per 1 min.	24,35±0,57	22,25±0,76	0,067
Cough, points	1,93±0,08	1,42±0,12	0,001
Shortness of breath, points	1,94±0,10	1,33±0,19	0,004
Sat O_2, %	91,56±0,53	92,75±0,53	0,244
Chest pain, points	1,73±0,07	0,83±0,16	<0,0001
Average number of hospitalization days	11,48±0,27	9,13±0,64	<0,0001

Note 1: statistical processing was performed using Student's T-test (for interval variables) and Mann-Whitney U-test (for ordinal variables);

Note 2: the data represent the values of error probability (p) obtained when comparing groups.

The mean values of the main CAP criteria in percentage and score measurements among the respondents of the main group depend on the presence of CMVI-persistence (studied by verification of Ig G CMV). Thus, in patients with CAP in the presence of Ig G CMV, the mean cough was (1.93 ± 0.08) points against (1.42 ± 0.12) points at p = 0.001 in patients without positive markers of viral persistence, indicating aggravating effect of CMVI on the course of CAP. Accordingly, the dynamics of mean values of dyspnea (p = 0.004), chest pain (p <0.0001) were characterized. The average respiratory rate tended to increase among patients with CMV persistence and was (24.35 ± 0.57) / min versus (22.25 ± 0.76) /

min among CMV-negative respondents (p = 0.067). When studying a similar average value of the saturation index according to the presence of persistence, statistical probability was not found (p = 0.244). In addition, the presence of CMV persistence with a high degree of statistical probability increases the inpatient stay for the patient with CAP: the mean number of hospitalization days for the CMV-positive respondent was (11.48 ± 0.27) days, whereas for the CMV-negative patient with CAP - (9.13 ± 0.64), p <0.0001.

We also analyzed the relationship of objective examination data of patients with CAP with the presence of CMVI persistence. The data of this analysis is presented in table. 4.

Table 4 - The average values of the data of objective examination of patients with CAP according to the Ig G CMV verification

Index, (M±m)	Ig G CMV		p
	Positive	Negative	
Number of affected lung segments	2,75±0,14	1,88±0,17	0,002
Intensity of dulling of percussion sound, points	1,96±0,07	1,38±0,12	<0,0001
Expressiveness of crepitation, points	0,68±0,05	0,42±0,10	0,020
The severity of dry wheezing, points	0,14±0,03	0,08±0,06	0,498
The severity of wet rales, points	0,60±0,06	0,38±0,10	0,047
The severity of pleural friction, points	0,09±0,03	-	0,139
Temperature, ºC	38,63±0,09	38,15±0,16	0,013

Therefore, based on the data obtained from table. 4, we see that among patients with CAP with verified CMVI-persistence, the average values of the number of lung segments impression (p = 0.002), the intensity of dulling of percussion sound (p <0.0001), the severity of wet rales (p = 0.047) and crepitation (p = 0,020), hyperthermia (p = 0,013) is higher compared to similar values in patients with CAP without Ig G CMV in serum. The average severity of dry wheezing in the comparison groups was almost indistinguishable (p = 0.498). However, noticeable was the fact that among patients with CAP with viral persistence, the mean expressiveness of pleural friction was (0.09 ± 0.03) points, whereas in the other group of patients it was not determined (p = 0.139). Summarizing the above, we can say that the persistence of CMVI has a large negative impact on the course of CAP in a given cohort of patients, which may have the connection with immunosuppression.

Subsequently, we analyzed the mean values of clinical course of CAP in patients with CMVI-persistence, depending on the limitation of CMVI-persistence (Table. 5).

Table 5 - Mean values of clinical course of CAP according to avidity Ig G CMV

Index, (M±m)	Ig G CMV-avidity				
	CMVI-negative (n=24)	1-39% (n=7)	40-60% (n=23)	>60% (n=51)	Total among CAP patients (n=105)
Respiratory rate per 1 min.	22,25±0,76	23,00±2,17	22,87±0,91	25,20±0,75	23,87±0,48 p=0,057
Cough, points	1,42±0,12	1,71±0,18	2,00±0,14	1,92±0,10	1,81±0,07
Shortness of breath, points	1,33±0,19	1,86±0,34	1,87±0,15	1,98±0,14	1,80±0,09 p=0,039
Chest pain, points	0,83±0,16	1,57±0,20	1,74±0,13	1,75±0,09	1,04±0,06 p<0,0001
Sat O_2, %	92,75±0,53	92,43±1,91	92,61±1,02	90,96±0,66	91,83±0,43 p=0,275
Number of affected lung segments	1,88±0,17	2,57±0,53	2,87±0,27	2,73±0,18	2,55±0,12 p=0,019
Intensity of dulling of percussion sound, points	1,38±0,12	2,00±0,22	1,91±0,12	1,98±1,0	1,83±0,07 p=0,002
Expressiveness of crepitation, points	0,42±0,10	0,43±0,20	0,70±0,10	0,71±0,06	0,62±0,05 p=0,058
The severity of dry wheezing, points	0,08±0,06	0,29±0,18	0,22±0,09	0,08±0,04	0,12±0,03 p=0,185
The severity of wet rales, points	0,38±0,10	0,57±0,20	0,65±0,10	0,59±0,07	0,55±0,05 p=0,241
The severity of pleural friction, points	-	0,14±0,14	-	0,12±0,05	0,07±0,02 p=0,106
Systolic blood pressure, mm Hg	117,92± 3,1	124,29± 3,7	124,57±3,8	122,25± 2,9	121,90±1,8 p=0,639
Diastolic blood pressure, mm Hg	71,58±3,6	73,43±4,2	76,52±2,3	73,22±1,7	73,58±1,3 p=0,628
Puls / min.	91,92±1,78	93,29±3,36	86,96±2,97	95,53±1,97	92,68±1,28 p=0,072
Temperature, ºC	38,15±0,16	38,71±0,21	38,80±0,18	38,54±0,12	38,52±0,08 p=0,049
Average number of hospitalization days	9,13±0,64	12,29±0,89	11,70±0,67	11,270±0,29	10,94±0,27 p=0,002

Due to the obtained data (table 5) regarding the dependence of the severity of clinical course of CAP in young people, depending on the degree of severity of CMVI-persistence, we tend to increase the average values of respiratory rate (from [23,00 ± 2,17] / min to [25,20 ± 0,75] / min at p = 0,057), pulse rate (from [93,29 ± 3,36] beats / min to [95,53 ± 1,97] beats / min at p = 0,072) , the severity of crepitus (from [0.43 ± 0.20] points to [0.71 ± 0.06] points at

p = 0.058). The deterioration in the clinical and diagnostic picture of CMV-positive respondents with CAP was also statistically significant, which deepened with increasing avidity of CMV antibodies, and therefore directly depended on the duration of CMV-persistence. Thus, the mean scores of the severity of clinical symptoms of CAP, such as the average value of hyperthermia (p = 0,049), the severity of percussion changes (p = 0,002), chest pain (p <0,0001), shortness of breath (p = 0,039), cough (p = 0.011), which indicate a more severe clinical course of CAP, increased according to the CMVI class of limitation (determined by the degree of avidity).

Conclusions

1. Persistence of CMVI is associated with the incidence of CAP.
2. The level of CMVI persistence increases according to the severity of the CAP (by PORT score).
3. Clinically significant symptoms of CAP (cough, purulent sputum, fever, shortness of breath) are more pronounced in patients with verified CMVI persistence as opposed to those without IgG CMV in serum, and their severity increases according to antibody content (persistence level) and directly depende on the duration of CMVI persistence.
4. The analyzing the expressiveness of the mean values of clinical course of CAP showed that their increase was observed among patients with verified CMVI, which was especially characteristic for the respondents with moderate and high levels of CMV IgG avidity.

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