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# CHARACTERISTICS OF HIV-ASSOCIATED DISEASES OF THE CENTRAL NERVOUS SYSTEM IN OLDER PEOPLE

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*SUMMARY.* ***The aim*** *of the work is to study the main characteristics of HIV-associated diseases of the central nervous system in persons over 50 years old and to determine the frequency and relationship of chances of development of neurological diseases depending on age aspects.*

***Patients and methods.*** *A retrospective analysis of 428 medical cards of patients with HIV-associated CNS diseases who were treated at the departments of Dnipropetrovsk regional and municipal AIDS centers in the period from 2010 to 2016 was conducted. Central nervous system diseases included cerebral tuberculosis, toxoplasmosis, fungal infections, neoplasms, encephalitis caused by Epstein-Barr virus, progressive multifocal leukoencephalopathy; cognitive impairments were analysed separately. The main study group included 51 patients (11.9 %) over the age of 50 years, the comparison group consisted of persons younger than 50 years old – 377 patients (88.1 %). Statistical processing of the results of the study was conducted using the programs STATISTICA v.6.1® and SPSS v.13. Levels of CD4 cell count and RNA HIV viral load were taken into account during the development of neurological diseases.*

***Results.*** *In the group of patients over 50, a tendency to a higher mortality rate was determined – 52.9 % vs. 43.0 % in the younger group (p=0.229 FET). In majority of the patients in the main group (52.9 %) HIV infection was diagnosed during visits due to neurological symptoms. The average time from the detection of HIV to the development of neurological symptoms was lower than in the comparison group, respectively 0.0 (IQR 0.0-2.5) years and 1.0 (IQR 0.0-6.0) years (p=0.012 W). The majority of patients in the main group had sexual route of transmission (61.8 %), whereas in the comparator group, the majority of patients (62.0 %) were infected during intravenous drug usage (p=0.009 FET). Antiretroviral therapy in the main group was received by significantly fewer patients – 23.5 % vs. 40.3 % in the comparison group (p=0.022 FET). The patients in the main group did not show statistical differences with the comparison group regarding CD4 cell count level – respectively 48.5 (IQR 15.25-206) cells/μL and 65.0 (IQR 20.75-175.25) cells/μL (p=0.601 U), while the median VL of the HIV RNA was 1.2 times higher in this group – 5.72 (IQR 4.74-5.89) copies/ml versus 4.9 (IQR 2.03-5.61) copies/ml (p=0.047 U).*

*In the structure of CNS diseases in both groups, tuberculosis of the central nervous system predominated. The age correlations with HIV-associated cognitive impairment, progressive multifocal leukoencephalopathy and the risk of developing of cerebrovascular disease (Stroke) have been identified. The chances of development of cognitive disturbances in patients over the age of 50 were 4.26 (95 % CI 2.29-7.93) times higher than in younger HIV-infected patients. It was also found that in this group, cognitive disturbanceswith the background of ART were more frequently diagnosed than in the comparison group (58.3 versus 25.0 %, p=0.020 FET). Patients older than 50 years of age were also more likely to be diagnosed with EBV-encephalitis (p=0.052 FET), the probability of development of which in this group was 2.24 (95 % CI 1.04-4.84) times higher than in the comparison group.*

***Conclusions.*** *The obtained data testify to the features of HIV-associated diseases of the CNS in patients over the age of 50 years. In this age group, the number of people infected with sexualroute of transmission was significantly higher than among younger people, the HIV infection was diagnosed later and, accordingly, fewer patients received ART. At the time of the development of neurological diseases in patients over 50, a higher level of RNA HIV viral load was observed in the absence of statistically significant immunological differences. In this group, high chances of developing PML, EBV-encephalitis, cognitive impairment,*

*and a tendency towards higher incidence of stroke are identified, which can lead to severe consequences, and underlines the importance of a more detailed consideration of the age aspect.*

***Key words:*** *HIV-infection, HIV-associated diseases of the central nervous system, age, cognitive impairment.*

Aging of the population is now becoming a global medical and social problem in many countries of the world. It is estimated that the number of HIV-positive people over the age of 50 in developed countries is over 10 %. It is expected that this percentage will continue to increase due to the improvement in the life expectancy of patients assigned to highly active antiretroviral therapy (HAART) [1]. Given the growing number of elderly people infected with HIV, there is a growing need for a study on the relationship between HIV and aging. Thus, it is suggested that active antiviral therapy and long life expectancy of patients can lead to a number of risks affecting quality of life, and such manifestations of aging as psychiatric diseases, neurocognitive disorders, metabolic and hormonal dysfunctions may depend on the chronic effects of HIV and/or therapy HIV [2].

It is believed that aging and HIV have a complex effect on immune cell dysfunction, which includes decreased phagocyte activity, cytolytic function of natural killer cells, expression of toll-like receptors and interleukin-12 production [3]. Elderly people are generally less likely to be suggested HIV testing than younger ones, which often leads to much later diagnosis of HIV infection in this category. Studies conducted by several authors have shown that in elderly patients at the time of diagnosis of HIV, the number of CD4 + lymphocytes is lower than that of younger people [4]. At the same time, data on possible differences in the level of viral load at the onset of treatment and the virological response to HAART in elderly and younger patients are contradictory in various studies [4, 5, 6]. According to the literature, decreased level of neurocognitive functioning in elderly patients is a major predictor of decreased adherence to ART and, accordingly, the risk of ART failures at the age of 50 years and older is generally associated with neurocognitive status. [7]. Since age can affect the progression of HIV infection and the structure of comorbid conditions, careful study of the specificities of the development of HIV-associated neurological diseases in older patients is required for more effective prediction and diagnosis, as well as the proper differential diagnosis of these diseases with age-related changes in the nervous system [8, 9].

**Aim** – to study the main characteristics of HIV-associated CNS diseases in persons over 50 years of age and to determine the frequency and ratio of odds ratio of development of neurological diseases depending on age aspects.

## Patients and methods

The study encompassed retrospective analysis of 428 medical records of adult patients with HIV-associated CNS diseases that were hospitalized and treated at the departments of the Dnipropetrovsk regional and municipal AIDS prevention and management centers in the period from 2010 to 2016, with appropriate records in medical charts. The study included HIV-positive patients aged 19 to 67 years with the most common diseases of the central nervous system in the Dnipropetrovsk region, including cerebral tuberculosis, toxoplasmosis, fungal etiology (candidiasis and cryptococcosis were grouped together), neoplasms, encephalitis caused by Epstein-Barr virus (EBV), progressive multifocal leukoencephalopathy (PML), stroke and encephalitis of unspecified etiology. In addition, the above mentioned diseases of the central nervous system, which were accompanied by cognitive impairments, were separately analyzed. The description of cognitive impairment was available in medical records. Levels of CD4 cell count and RNA HIV viral load were taken into account during the development of neurological diseases.

The main group of the study included 51 patients (11.9 %), over the age of 50 years. The comparison group included persons younger than 50 years old – 377 patients (88.1 %).

The statistical processing of the research results was carried out using the application packages STATISTICA v.6.1® and SPSS v.13. The parametric and nonparametric characteristics and comparison methods were used for the normal distribution law (Shapiro-Wilk's W test): for the normal distribution law, the arithmetic mean (M), standard error (m), Independent-Samples T-Test (T) ; in other cases, the median (Me), the interquartile range (IQR), the Mann-Whitney U Test (U) criterion. Comparison of relative indices was performed on two-tailed Fisher's Exact Test (FET). In order to compare the incidence of HIV-associated CNS diseases and cognitive impairment in groups, odds ratios (ORs) with confidence intervals (95 % CI) were determined.

## Results and discussion

The average age of patients in the main group during the development of neurological diseases was (52.96±0.49) years, median (Me) – 52 (IQR 50-54) years. In the comparison group, these figures were – (36.7±0.30) years, Me – 37.0 (IQR 33-41) years. As can be seen from Table 1, the main group and the comparison group were statistically comparable in the sex of patients with prevalence of males – 64.7 % and 57.0 %, respectively, in groups (p=0.365 FET), and also in the level of CD4 cell count – 48.5 (IQR 15.25-206) cells/μL and 65.0 (IQR 20.75-175.25) cells/μL (p=0.601 U). A tendency towards a higher mortality rate in

the main group was noted – 52.9 % vs. 43.0 % in the younger age group (p=0.229 FET). Most (52.9 %) of patients over 50 years of age were found late in the period of the diagnosis of neurological diseases, which corresponded to the 4th clinical stage of HIV infection. The mean time from the time of HIV detection to the development of neurological symptoms in the main group was lower than in the comparison group, respectively, 0.0 (IQR 0.0-2.5) years and 1.0 (IQR 0.0-6.0 ) years (p=0.012 U) (Table 1).

Table 1

Characteristics of patients with HIV-related CNS diseases older than 50 years and older

| Characteristics | | The comparison group | The main group | The significance of the differences between the group |
|---|---|---|---|---|
| | | <50 years | ≥50 years | |
| Male sex, n (%) | | 215 (57.0 %) | 33 (64.7 %) | p=0.365 FET |
| Fatal cases, n (%) | | 162 (43.0 %) | 27 (52.9 %) | p=0.229 FET |
| HIV transmission pathway, number of patients in % | parenteral (IDU) | 62.0 % | 38.2 % | p=0.009 FET |
| | sexual | 38.0 % | 61.8 % | |
| Theaveragedurationoftheperiodfromtheestablishmentof HIVstatustothedevelopmentofneurologicalsymptoms, Me (IQR), years | | 1.0 (0.0–6.0) | 0,0 (0.0–2.5) | p=0.012 U |
| CD4 cell count in the development of neurological diseases, Me (IQR), cells / mm$^3$ | | 65.0 (20.75–175.25) | 48.5 (15.25-206) | p=0.601 U |
| Lg RNA HIV viral load during the development of neurological diseases, Me (IQR), copies / ml | | 4.9 (2.03–5.61) | 5.72 (4,74-5.89) | p=0.047 U |
| Patients who received ART, n (%) | | 152 (40.3 %) | 12 (23.5 %) | p=0.022 FET |

Patients older than 50 years of age (the main group) had the prevalence of sexually transmitted infections (61.8 % of patients), while in the comparison group, the majority of patients (62 %) were infected with intravenous drug use (p=0.009 FET). Antiretroviral therapy (ART) covered 40.3 % of patients under the age of 50 years and only 23.5 % of patients in the main group (p=0.022 FET), which correlated with a short period of follow-up. At the same time, the median lg RNA of HIV viral load in them was 1.2 times higher than in younger patients – 5.72 (IQR 4.74-5.89) copies/ml versus 4.9 (IQR 2.03-5.61) copies/ml at p=0.047 U.

In the structure of CNS diseases (Table 2), in patients of the main group, as well as among young people, CNS tuberculosis dominated.

Table 2

Frequency and proportion of chances of development of HIV-associated neurological diseases in patients older than 50 years old

| CNS Diseases | Comparison Group | Main group | | Significance of differences between groups, p (FET) |
|---|---|---|---|---|
| | <50 years | ≥50 years | | |
| | % | % | OR (95 % CI) | |
| Tuberculosis | 40.8 | 39.2 | 0.93 (0.51–1.70) | 0.880 |
| Fungal infection (yeast fungi) | 16.7 | 15.7 | 0.93 (0.42–2.07) | 1.00 |
| EBV-encephalitis | 9.8 | 19.6 | 2.24 (1.04–4.84) | 0.052 |
| Progressive multifocal leukoencephalopathy (PML) | 4.8 | 13.7 | 3.17 (1.26–8.02) | 0.020 |
| Toxoplasmosis | 26.8 | 21.6 | 0.75 (0.37–1.52) | 0.499 |
| Stroke | 1.6 | 3.9 | 2,52 (0.50–12.80) | 0.245 |
| Encephalitis unspecified | 13.0 | 5.9 | 0.42 (0.13–1.40) | 0.174 |
| Brain tumors | 1.1 | 0 | 0.99 (0.98–1,00) | 1.00 |
| The presence of cognitive impairment | 15.1 | 43.1 | 4.26 (2.29–7.93) | <0.001 |

Age associations with HIV-1-associated cognitive impairment, progressive multifocal leukoencephalopathy and the risk of developing cerebrovascular pathology (stroke) have been determined, which coincides with the literature [10]. As can be seen from Table 2, the chances of development of cognitive impairment in patients over the age of 50 were 4.26 (95 % CI 2.29-7.93) times higher than those of younger HIV-infected patients. It was found that in individuals in this group, cognitive impairment on the background of ART was more frequent than in the comparison group (58.3 versus 25.0 %, p=0.020 FET). The reasons could include some changes associated with aging, such as: selective destruction of neurons in the hippocampus [11], formation of amyloid plaques [12]; the toxic effect of drugs [2], as well as the limited penetration of some antiretroviral drugs through the blood-brain barrier [11, 13], which requires a detailed analysis of the composition of ART regimens and the determination of HIV viral load in the CSF. In the group over 50 years of age, PML was also more often diagnosed (p=0.020 FET). The risk of developing this disease in this group was 3.17 (95 % CI 1.26-8.02) times higher than that of younger people and may have been due to a higher viral load. Older patients also showed tendency to a higher incidence of stroke, which may be more closely related to age with an increase in the number of observations and greater age separation. Patients older than 50 years of age were more likely to be diagnosed with EBV-encephalitis (p=0.052 FET), the chances of which in this group were 2.24 (95 % CI 1.04–4.84) times higher than in the comparison group, which may be due to the fact that the aging immune system, even in people without HIV, is characterized by clonal expansion of CD8 + T cells and cannot control the reactivation of EBV and CMV [14]. It is also considered that the effect of age on the EBV-specific response depends on the serological status of CMV, so, in the seronegative to CMV patients, the response of CD8 to EBV cells significantly increases with age and results in the suppression of virus-specific immunity during aging [15]. These factors require further in-depth study of patients of older age with HIV infection and EBV infection.

## Conclusions

The obtained data testify to the peculiarities of HIV-associated CNS diseases in patients over 50 years of age. In this age category, the number of people infected by sexual route was significantly higher than among younger people. Persons older than 50 years were diagnosed with HIV later than younger ones and, accordingly, there was a lower coverage of ART. At the time of the development of neurological diseases, higher HIV RNA viral load was observed in the absence of statistically significant immunological differences. Patients over 50 have high chances of developing PML, EBV-encephalitis, cognitive impairment, and a tendency to higher incidence of stroke, which can lead to severe consequences and emphasizes the importance of more detailed consideration of age-related aspects, as well as rationalization of management in this group to improve the quality of life of patients.

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# ХАРАКТЕРИСТИКА ВІЛ-АСОЦІЙОВАНИХ ЗАХВОРЮВАНЬ ЦЕНТРАЛЬНОЇ НЕРВОВОЇ СИСТЕМИ В ОСІБ СТАРШОГО ВІКУ

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*РЕЗЮМЕ.* ***Мета роботи*** *– вивчити основні характеристики ВІЛ-асоційованих захворювань центральної нервової системи в осіб старше 50 років і визначити частоту і відношення шансів розвитку неврологічних захворювань залежно від вікових аспектів.*

***Пацієнти і методи.*** *Проведений ретроспективний аналіз 428 медичних карт пацієнтів з ВІЛ-асоційованими захворюваннями ЦНС, які перебували на лікуванні у відділеннях Дніпропетровського обласного та міського центрів СНІД в період з 2010 по 2016 роки. Захворювання ЦНС включали цереброваль-*

*ний туберкульоз, токсоплазмоз, ураження грибкової етіології, новоутворення, енцефаліти, які викликані Епштейна-Барр вірусом, прогресуючу мультифокальну лейкоенцефалопатію та окремо аналізувалися когнітивні порушення. До основної групи дослідження був включений 51 пацієнт (11,9 %), віком старше 50 років, групу порівняння склали особи молодші 50 років – 377 пацієнтів (88,1 %). Статистична обробка результатів дослідження проводилася з використанням програм STATISTICA v.6.1® и SPSS v.13. Показники CD4 cellcount и RNA HIV viralload враховувались у період розвитку неврологічних захворювань.*

***Результати.*** *У групі пацієнтів старше 50 років визначена тенденція до більшої летальності – 52,9 проти 43,0 % у групі молодших осіб (p=0,229 FET). У більшості (52,9 %) пацієнтів основної групи ВІЛ-інфекцію було діагностовано при зверненні з приводу неврологічних симптомів. Середній час від виявлення ВІЛ до розвитку неврологічних симптомів був нижчим, ніж у групі порівняння, відповідно 0,0 (IQR 0,0-2,5) і 1,0 (IQR 0,0-6,0) років (p=0,012 W). У пацієнтів основної групи переважав статевий шлях інфікування ВІЛ (61,8 %), а в групі порівняння – більшість пацієнтів (62 %) була інфікована при внутрішньовенному вживанні наркотиків (p=0,009 FET). Антиретровірусну терапію в основній групі отримувало значно менше пацієнтів – 23,5 проти 40,3 % у групі порівняння (p=0,022 FET). У пацієнтів основної групи не виявлено статистичних відмінностей з групою порівняння в рівні CD4 cellcount – відповідно – 48,5 (IQR 15,25-206) cells/μL та 65,0 (IQR 20,75-175,25) cells/μL (p=0,601 U) при тому, що медіана ВН РНК ВІЛ у них була в 1,2 разу вище – 5,72 (IQR 4,74-5,89) копій/мл проти 4,9 (IQR 2,03-5,61) копій/мл (p=0,047 U).*

*У структурі захворювань ЦНС в обох групах переважав туберкульоз ЦНС. Визначені вікові асоціації з ВІЛ-асоційованими когнітивними порушеннями, прогресуючою мультифокальною лейкоенцефалопатією та ризиком розвитку цереброваскулярної патології (Stroke). Шанси розвитку когнітивних порушень у пацієнтів старше 50 років були в 4,26 (95 % CI 2,29-7,93) разу вище, ніж у молодших ВІЛ-інфікованих пацієнтів. При цьому встановлено, що в осіб цієї групи когнітивні порушення на фоні прийому АРТ розвивалися частіше, ніж у пацієнтів групи порівняння (58,3 проти 25,0 %, p=0,020 FET). У пацієнтів старше 50 років також частіше діагностували ЕБВ-енцефаліти (p=0,052 FET), шанси розвитку яких у даній групі були в 2,24 (95 % CI 1,04-4,84) разу вище, ніж у групі порівняння.*

***Висновки.*** *Отримані дані свідчать про особливості ВІЛ-асоційованих захворювань ЦНС у пацієнтів старше 50 років. У даній віковій категорії число осіб, інфікованих статевим шляхом, було значно більше, ніж серед молодших осіб, ВІЛ-інфекцію було діагностовано пізніше і, відповідно, менша кількість пацієнтів отримувала АРТ. На момент розвитку неврологічних захворювань у пацієнтів старше 50 років спостерігався більший рівень RNA HIV viralload при відсутності статистично значущих імунологічних відмінностей. В даній групі визначені високі шанси розвитку ПМЛ, EBV-енцефалітів, когнітивних розладів і тенденцію до більшої частоти інсультів, що може призводити до тяжких наслідків, і підкреслює важливість більш детального обліку вікового аспекту.*

***Ключові слова:*** *ВІЛ-інфекція, ВІЛ-асоційовані захворювання ЦНС, вік, когнітивні порушення.*

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