THE MOST FREQUENT NEUROLOGICAL COMPLICATIONS IN HIV PATIENTS IN CONSTANTA AND THE INFLUENCE THAT COINFECTIONS HAVE IN THE ONSET OF SUCH CONDITIONS

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ABSTRACT

Abstract: This paper shows the results of a retrospective observational analytical study that has enrolled 166 HIV positive patients diagnosed with a neurological complication between June 2012 and June 2020, in Clinical Infectious Diseases Hospital of Constanta. 119 patients (71,69%) were diagnosed with one of the three neurological complications: HIV associated dementia (HAD), Progressive Multifocal Leukoencephalopathy (PML) and CNS Toxoplasmosis (CT). We have noted CD4 levels, viral loads, and the presence/absence of other infections like: HBV, HCV, Treponema pallidum, Mycobacterium Tuberculosis.

The results show that PML and CT, in this order, are the main opportunistic infections with important neurological impact. Both, PML and CT are in direct correlation with the immune status, but also with other infections like the infection with HCV or with M. Tuberculosis. CD4 nadir <100 cells/mm³ and viral load ≥100000copies/ml have a stronger association with PML ($p < 0,05$). Patients known with HIV and T. pallidum infection are more likely, in case of new sudden neurological signs, to be diagnosed with Neurotoxoplasmosis versus PML, or HAD ($p < 0,05$). Given the fact that HIV patients can have multiple alterations of neurological functions, and spectacular but complicated neuro imagistic results, knowing the history of the patients, the lab results, and the statistical probability can help the physician, infectious disease specialist or neurologist, to make a faster and precise diagnosis.

Keywords: HIV, Coinfections, HIV associated dementia, Progressive Multifocal Leukoencephalopathy, CNS Toxoplasmosis

Introduction

Even if the implementation of combined antiretroviral therapy (cART) across the world has prolonged life expectancy of most patients, neurological complications remain frequent. The patients that do not take cART are susceptible for opportunistic infections and malignancies; the patients that are virally suppressed with cART can develop metabolic complications and a high risk for HAD; the variably adherent patients are vulnerable to all the previous complications (Handbook of Clinical Neurology). In Constanta, we have long term HIV survivors, late presenters and also, we observe the “treatment fatigue

phenomenon”.

Worldwide prevalence of HBV coinfection could be estimated to be 5%–10% in persons living with HIV infection. (1). Chronic HBV advances faster to cirrhosis, end-stage liver disease, and liver cancer in people with HIV/ HBV coinfection than in people with only HBV infection(2). But chronic HBV doesn't appear to cause HIV to advance faster in people with HIV/ HBV coinfection (3,4).

Hepatitis C virus (HCV) infection occurs commonly among HIV-infected individuals, with approximately 20% of HIV-infected persons worldwide estimated to have concurrent chronic HCV infection (5).

HCV replication is enhanced in the presence of HIV coinfection, resulting in higher serum and liver HCV RNA levels. The rate of progression of fibrosis in HIV/HCV-coinfected patients is estimated to be 3 times higher than that in HCV-monoinfected patients (6). The influence of HCV infection on the natural history of HIV disease is a topic of dispute. HCV infection may negatively impact CD4 cell count restoration, and cirrhosis is associated with depressed CD4 cell counts, independent of HIV or HCV infection (7). Apparently, hepatitis C potentiates HIV-1 neurotoxicity(8).

Epidemiologic studies demonstrate that sexually transmitted diseases (STDs) including syphilis, and particularly genital ulcers associated with primary syphilis, are associated with an increased risk of HIV acquisition (9,10). HIV patients have an eight-time higher risk of being serological syphilis positive, also (10). Early syphilis may decrease CD4⁺ T-cell counts (CD4 cell counts) and increase HIV RNA (11). Probably, the high prevalence of primary syphilis in HIV positive patients, it's generated by the inability to control the CNS infection and less by the high rate of CNS infection (12).

Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive individuals (13) and it remains the most common cause of death in patients with AIDS (14). Both, TB and HIV cause immunodepression with low CD4 cells counts (15).

Materials and methods

166 HIV positive patients diagnosed with a neurological complication were enrolled in the study between June 2012 and June 2020. The data was collected from the observational charts from Clinical Infectious Diseases Hospital of Constanta.

The experimental data were processed with IBM SPSS statistics 23 software. The procedures used were: descriptive statistics, graphs, parametric statistical tests, nonparametric statistical tests for categorical data (χ^2 association test, with OR calculation, χ^2 test for comparison of two proportions) and nonparametric statistical tests for ordinal data (Mann-Whitney U test, Kruskal-Wallis test).

The patients with HAD were the patients presented with memory loss, psychomotor latency or loss of attention or concentration.(16). From this group were excluded the patients with CNS opportunistic infections, cranio-cerebral trauma, drug abuse or alcohol abuse in the last 6 months. The international HIV associated Dementia Scale (IHDS) and PAOFI test (for auto evaluation of daily functions) were performed.

In the HAD group were selected the patients with less than 10 points or 10 points as a result of IHDS. The cut-off for PAOFI was 99 points and all the patients scored more than 99 points.

Results

The 3 most common neurological complications in this study were: HAD (65 patients, 39,16%), PML (38 patients, 22,89%) and CT (16 patients, 9,64%).

Table 1 shows for how long HIV infection was known for these patients, at the moment of the neurological complication diagnosis-HAD, PML or CT.

Table 1 Analysis of HIV infection duration

The interval (years) from HIV diagnosis to the diagnosis of the neurological complication	Type of neurological complication		
	HAD	TC	PML
N	65	16	38
Mean	13.03	8.81	12.58
Median	12.00	10.50	13.00
Mode	10.00	.00	.00
Std. Deviation	6.07	7.35	8.92
Minimum	.00	.00	.00
Maximum	24.00	20.00	28.00

The value of CD4 count at the moment of the neurological complications diagnosis had a mean value of 539, 14, median of 523 for HAD and for PML and CT the values are: mean 100,08, median 79,5 for PML and mean 167,06, median 65 for CT. The median values of CD4 cells count have a statistically significant difference between HAD and TC and between HAD and PML ($p < 0.001$, Independent Sample Median Test). The distribution of CD4 has a statistically significant difference between HAD and TC and between HAD and PML ($p < 0.001$, Kruskal-Wallis Test) (Figure 1).

Figure 1. Box-Plot representation for CD4 for all 3 diseases (HAD=HIV associated dementia, TC= CNS Toxoplasmosis, PML= Progressive Multifocal Leukoencephalopathy)

The median values of the viral load have also a statistically significant difference between PML and CT, PML and HAD ($p < 0.001$, Independent Sample Median Test). The distribution of viral load value (HIV RNA) has a statistically significant difference between PML and CT, PML and HAD ($p < 0.001$, Kruskal-Wallis Test).

When the three groups of patients were analyzed looking for the coinfections HIV-HBV or HIV-HCV the results were different. Even though 33 patients (27,7%) of a total of 119 tested positive for HBV there were no

statistically significant differences between the three groups. 8 patients (6,7%) were HCV positive, with statistically significant differences between proportions as seen in Table 2 .

“HCV” and “Type of neurological complication” are dependent variables: $\chi^2_{\text{calc}} = 7354$, $df = 2$, $p = 0.025 < \alpha = 0.05$ (Chi-Square Test).

Regarding the coinfection HIV-T. Pallidum, the results showed statistically significant differences between the proportion of patients with HAD and positive VDRL and the proportion of patients with CT and positive VDRL ($p < 0,05$). Also, statistically significant differences were found between the proportion of patients with CT and positive VDRL and the proportion of patients with PML and positive VDRL ($p < 0,05$).

29 patients (24,4%) from the total of 119 patients have TB in the medical history. There are statistically significant differences between the proportion of patients with HAD and TB and the proportion of patients with CT or PML and TB ($p < 0,05$). (Table 3)

Discussions

The 3 most common neurological complications in our study are the same as the ones seen in 2010 in the study from UK, but in a different order of frequency. In the British cohort

Table 2 Analysis of the type of neurological complication of HIV disease and HCV (HAD=HIV associated dementia, TC= CNS Toxoplasmosis, PML= Progressive Multifocal Leukoencephalopathy, HCV= Hepatitis C virus)

			Type of neurological complication			Total
			HAD	CT	PML	
HCV	Positive	Count	1a	3b	4a, b	8
		% within Type of neurological complication	1.5%	18.8%	10.5%	6.7%
	Negative	Count	64a	13b	34a, b	111
		% within Type of neurological complication	98.5%	81.2%	89.5%	93.3%
Total		Count	65	16	38	119
		% within Type of neurological complication	100.0%	100.0%	100.0%	100.0%

Table 3 Analysis of the type of neurological complication of HIV disease and TB (HAD=HIV associated dementia, TC= CNS Toxoplasmosis, PML= Progressive Multifocal Leukoencephalopathy, TB= Tuberculosis)

			Type of neurological complication			Total
			HAD	CT	PML	
TB	Positive	Count	4a	8b	17b	29
		% within Type of neurological complication	6.2%	50.0%	44.7%	24.4%
	Negative	Count	61a	8b	21b	90
		% within Type of neurological complication	93.8%	50.0%	55.3%	75.6%
Total		Count	65	16	38	119
		% within Type of neurological complication	100.0%	100.0%	100.0%	100.0%

study, CT was the second diagnosis and PML the third. In our study, with a smaller number of patients than the one in UK, PML was the second diagnosis as percentage from total, and the third was CT (17). In another study from China, that enrolled only 60 patients with neurological conditions, the results are very different. In order of the frequency, we find Cryptococcal meningitis with the biggest percentage 22%, followed by CT with 17% and in the third place CNS TB (11,7%) (18). We have compared very different groups of patients, with very different number of patients enrolled, and different methods of working with the data. We have to bear in mind that we are looking mostly at opportunistic infections and we can understand better the results if we think at the geographically epidemiological discrepancies between Europe and Asia.

Most of the patients have had the HIV infection diagnosis for many years before the diagnosis of the neurological condition (Figure 1). All three diseases, HAD, PML, TC are diagnosed, usually, in advanced stages of HIV-AIDS, and are also, AIDS-defining clinical conditions (19).

A low CD4 cell count is correlated with a poor immunological status so this is why we see the statistical correlation between CD4 cell count and opportunistic infections, and a weak correlation between CD4 and cognitive decline. Cognitive decline is insidious, can be diagnosed in different stages and is associated with the classic factors for the severity of the disease like CD4 cell count, CD4 nadir, great duration of HIV infection, medical history of AIDS-defining clinical conditions, viral load, but also other factors are very important like vascular and metabolic factors (20).

In our study, the highest viral load can be found in PML patients, with statistical differences between them and the patients with HAD or with CT. Knowing that the viral load is the parameter used to monitor the efficiency of cART, we can say that the patients with PML are the ones with the worst therapeutic response. One of the major problems, nowadays, being the poor adherence to the treatment of adult HIV patient that have been in treatment for more than 20 years. This is one of the reasons why debilitating or fatal conditions like PML still affect HIV positive patients.

In our study, there are no statistical differences generated by the coinfection HIV-HBV, so we can say that our results are more inclined to agree with other studies results, that did not find an important influence of HBV on CNS of patients with HIV (3, 4). On the other hand, the coinfection HIV-HCV was found, in this study, in correlation with PML and CT and less with HAD. So, it seems like HCV has a negative impact on CD4 cell count (7), and this explains the vulnerability of this patients to opportunistic infections like PML or CT.

The results of the study, also, show the association between medical history of syphilis and CT. *T. pallidum* and *T. gondii* attach to host tissues via the extracellular matrix component, laminin. Laminin is the major glycoprotein found within basement membranes (21,22). Probably, the association between *T. pallidum* and *T. gondii* in HIV positive patients, in this study, can be explained by the similar pathogenic mechanism.

Tuberculosis in a HIV infected patient, stimulates the disease progression, probably by prolonged immunological activation (23). Both, TB and HIV cause immunodepression with low CD4 cells counts (15). In this context, in our study, TB was associated with PML and TC and less correlated with HAD.

Conclusions

Progressive Multifocal Leukoencephalopathy being more frequent than CNS Toxoplasmosis, differentiate our study from similar ones conducted in Europe. This shows an efficient anti toxoplasmosis prophylaxis, but also it calls for attention because, PML is a severe neurological condition and we need to work more for the prevention and treatment of this disease.

CNS Toxoplasmosis and Progressive Multifocal Leukoencephalopathy are still the most frequent opportunistic infections, in correlation with a severe HIV/SIDA disease parameters (long disease duration, low CD4 cell count, high viral load levels) and also associated with HCV or/and *M. Tuberculosis* coinfection.

Patients with HIV and *T. pallidum* infection are more likely, in case of new sudden neurological signs, to be diagnosed with Neurotoxoplasmosis versus PML or HAD.

Patients with HIV infection and neurological signs or symptoms are complex patients, that need special attention from a neurologist regarding the medical history, neurological examination, lab investigations and neuro imaging findings, so it is important to know what to expect in a certain medical context, which condition to suspect first, in order for the patient to have the most efficient medical care.

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