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Neurological complications associated with HIV infection

- SUMMARY -

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Introduction

Neurological pathology is an important burden for HIV-infected patients, while the accumulation of neurological conditions in this context becomes much more complex as we move away from the first findings of cases, and patients age as access to antiretroviral therapy is easy.

In this context, we are committed to explore, expose and analyze a group of patients with neurological complications at the Constanța facility, with the clearly defined purpose of knowing in order to help.

1. Neurological complications of HIV infection - general data

BRAIN		
Predominantly non-focal	Predominantly focal	Cerebrovascular disorders
AIDS dementia complex (subacute / chronic HIV encephalitis)	Cerebral toxoplasmosis	Mostly nonbacterial endocarditis, cerebral hemorrhages associated with thrombocytopenia and vasculitis
Acute HIV encephalitis	Primary CNS lymphoma	
Cytomegalovirus encephalitis	Progressive multifocal leukoencephalopathy	
Cryptococcal varicella-zoster virus encephalitis	Cryptococcoma	
Encephalitis with herpes simplex virus	Cerebral abscess / tuberculoma	
Metabolic encephalopathies	Neurosyphilis (meningovascular)	
SPINAL CORD		
Vacuolar myelopathy		
Herpes simplex or zoster myelitis		
MENINGES		
Aseptic meningitis (HIV)		
Cryptococcal meningitis		
Tuberculous meningitis		
Syphilitic meningitis		
Metastatic lymphomatous meningitis		
NERVOUS ROOTS AND PERIPHERAL NERVES		
Infections		
Shingles		
Lumbar polyradiculopathy with cytomegalovirus, by viral or immunological mechanism		
Acute or chronic inflammatory HIV polyneuritis		
Mononeuritis multiplex		
Sensory-motor demyelinating polyneuropathy		
Painful distal sensory polyneuritis		

Diffuse infiltrative lymphocytic syndrome (DILS)
MUSCLES
Polymyositis and other myopathies (including drug-induced myopathies)

Source: Adapted courtesy of Brew B, Sidtis J, Petito DK, Price RW: The neurological complications of AIDS and human immunodeficiency virus infection, in Plum F (ed), Advances in Contemporary Neurology. Philadelphia, Davis, 1988, chap. 1.

2. Primary infection with human immunodeficiency virus type 1 (HIV-1) and neurological sequelae

Primary infection with human immunodeficiency virus type 1 (HIV-1) is defined as the time elapsed from initial HIV infection to complete seroconversion [11]. Patients may be asymptomatic during the first infection, and those who are symptomatic may benefit from an early diagnosis of HIV and the possibility of starting antiretroviral therapy in the early stages. During primary HIV infection, the entire nervous system may be affected and patients may experience headache, suffer from meningoencephalitis, epileptic seizures, acute disseminated encephalomyelitis, movement disorders, optic neuritis, myelitis, paresis of cranial nerves (especially facial nerve damage), neuritis of brachial plexus, sensitive polyneuropathy, Guillain-Barre-like polyneuritis, acute rhabdomyolysis [12].

3. The HIV reservoir in the central nervous system

HIV reaches the CNS level early during primary infection [14]. There is also a compartmentalization of HIV DNA with an independent population at the CNS level [15]. It is possible that the mechanisms initiated during this primary infection actually explain the increased frequency of HAND despite cART [21, 22], hence once again the importance of diagnosing primary infection and possibly preventing the formation of the CNS reservoir.

4. HIV-associated neurocognitive disorder

Despite cART treatment and the ongoing attempt to perform immunovirological control, about half of HIV-positive patients suffer from cognitive decline [24, 25, 26, 27, 28].

An attempt was made to stage the cognitive impairment by proposing the Frascati criteria in 2006 [30]. They divide patients into three categories: asymptomatic neurocognitive disorder (ANI), mild cognitive decline (MND) and HIV-associated dementia (HAD) depending on the results of neuropsychological tests and the degree of impairment of daily functionality.

Although there is a correlation with the value of CD4, viral load and time elapsed since HIV infection, it is not possible to say which of the patients will develop HAND (HIV-Associated Neurocognitive Disorder). The insidious onset and varied symptoms also make HAND diagnosis difficult. In this context, several screening tests have been proposed, although there is no consensus on when and how often to use them [81]. Given the limited resources, performing screening tests on asymptomatic patients remains a controversial issue [81].

Drugs that cross the blood-brain barrier could reduce the viral reservoir in the CNS and thus viral replication and inflammation leading to HAND. The efficiency of CNS penetrability was scored (CPE), the higher the score the better the CNS penetrability. A score of the effectiveness of the action on monocytes was also proposed, considering the high score that of viral agents that can prevent HAND [161].

Given the associated vascular pathology, the importance of control over the vascular risk factor should also be emphasized.

5. Progressive multifocal leukoencephalopathy (LEMP, PML)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by the John Cunningham virus (JCV). PML is characterized by infection of glial cells, i.e., infection of oligodendrocytes and astrocytes. It occurs in the context of immunosuppression and increases morbidity and mortality.

Immune Reconstitution Inflammatory Syndrome

The acronym IRIS refers to the paradoxical, clinical deterioration that occurred in a patient diagnosed with a pre-existing infectious disease, as a result of introducing the appropriate treatment. IRIS often occurs in immunocompromised patients, predominantly in the context of HIV / AIDS, but is not limited to this disease, and describes the situation in which a pathogen of relatively low virulence causes a significant infectious load. With immune reconstitution (often combined with targeted anti-infective treatment), the host becomes able to provide a substantial immune response, consequently, the inflammatory response becomes so obvious that a temporary worsening of the general state can occur. Most cases of PML with IRIS stabilize or improve over a few weeks or months. However, fulminant IRIS can lead to a significant degree of morbidity, and fatal cases are also reported.

6. Cerebral toxoplasmosis

Toxoplasmic encephalitis remains the most common cause of space-occupying intracerebral masses in individuals with HIV infection [284, 285]. Persons who are IgG-seropositive for Toxoplasma, who have CD4 + T cell concentrations below 200 / ml in peripheral blood, and those who are not treated with trimethoprim-sulfamethoxazole, have a high risk of developing toxoplasma encephalitis [286, 287, 284, 288].

7. Cryptococcal meningitis

Cryptococcal meningitis is the most common life-threatening fungal infection among HIV-positive patients, with an estimated 1 million symptomatic and diagnosed infections and 60,000 deaths annually [313].

8. HIV infection and stroke

Stroke is a complication of HIV infection that does not define AIDS and has become more common in an aging population [335].

9. Neuromuscular complications of HIV infection

Increased survival expectancy rate has led to an increase in the prevalence of chronic neuromuscular diseases [364, 365]. The category of neuromuscular complications of HIV infection includes: distal symmetrical polyneuropathy (PSD), toxic antiretroviral neuropathy, acute demyelinating inflammatory polyneuropathy (PIDA) or chronic demyelinating inflammatory polyneuropathy (PIDC), multiplex mononeuropathy, progressive HIV neuropathy, vegetative neuropathy.

10. Primary cerebral lymphoma

Primary cerebral lymphoma (PCL) has been known as one of the defining diseases of AIDS since 1983 and accounts for up to 15% of non-Hodgkin's lymphomas found in HIV-positive patients. Most PCLs in this context are directly correlated with the existence of Epstein-Bar virus (EBV) infection [410, 411].

11. Cytomegalovirus (CMV) infection

CMV can cause encephalitis, which can be associated with focal lesions of the CNS, ascending polyradiculoneuritis or polyradiculomyelitis, polyneuropathy and, less frequently, vasculopathy with stroke (CVA).

12. Tuberculous meningitis

Mycobacterium tuberculosis infection can cause a variety of nervous system conditions including: meningitis, associated or not with hydrocephalus or vasculitis, tuberculoma, tuberculous abscess and polyradiculoneuritis or polyradiculomyelitis. Tuberculous meningitis is the most common form of infection of the nervous system caused by M. tuberculosis and is responsible for about 1% of all cases of tuberculosis [457].

13. Herpes simplex encephalitis

The most common neurological condition caused by the herpes simplex virus (HSV) 1 is encephalitis, and HVS-2 is meningitis, although encephalitis caused by HSV-2 is a well-defined entity. Although herpes simplex encephalitis is the most common type of sporadic encephalitis in the general population, in HIV-positive patients the frequency is much lower. In several large studies, HSV-associated neurological disease was found in only 3% of patients [510, 511, 512, 513].

14. Neurocysticercosis

Neurocysticercosis (NCC) is the most common parasitic CNS infection [517]. NCC lesions can be located anywhere in the CNS and can be observed at various anatomopathological stages [518]. A clear predilection for certain brain regions has not been determined, although there are authors who claim that the most affected regions are the cortex and basal ganglia [519].

15. Objectives and model of the study

The aim of this study is to evaluate the neurological complications associated with HIV, which occurred in patients registered with the Constanta Regional HIV / AIDS Treatment Facility, one of the centers in Romania where approximately 1000 patients are being monitored.

The study followed an analytical, observational, retrospective design, and was conducted at the Clinical Hospital for Infectious Diseases Constanța, within the Clinical Center of Excellence for the treatment of HIV-infected patients.

The objectives were as follows:

Determine the main neurological complications that alter the course and quality of life of HIV-infected patients, in the records of the Constanța regional center.

Correlation of the main neurological diseases related to HIV with risk factors and evaluation of the significance of risk factors, comparatively, for these diseases.

Highlight risk factors correlated with mortality from HIV-related neurological complications in patients in the study.

16. General methodology

All patients who suffered from neurological complications associated with HIV infection in the period June 2012-June 2020 were included in the study. We collected both patient's consultation sheets at the HIV Department of the Clinical Hospital for Infectious Diseases Constanța, and monitoring and registration sheets existing at the Clinical Center of Excellence for the treatment of HIV-infected patients, Constanța.

The following data relevant to the study were extracted from the documents: type of nervous system disease, age at diagnosis of neurological complication of HIV, sex (male / female), year in which the diagnosis of neurological complication was established, origin of patients (rural / urban), the year in which the diagnosis of HIV infection was established, the route of HIV transmission, the age at which the HIV-positive diagnosis was established, the CD4 value at the time of diagnosis of HIV infection, the CD4 nadir value, the viral level at the diagnosis of neurological complication B (HBV), hepatitis C virus (HCV), Treponema pallidum or Mycobacterium tuberculosis, whether or not the patient is undergoing ARV treatment at the time of diagnosis of the neurological complication, whether the neurological condition was the inaugural diagnosis for HIV infection, neurological clinical manifestations, the number of ARV treatments the patient went through until diagnosis, the neurological complication, the classes of ARV drugs that make up the therapy, if and when these patients died.

The data were processed using the IBM SPSS Statistics 23 statistical processing program. The procedures used were: Descriptive statistics (for characterizing discrete and continuous variables defined at the database level), Graphs, Parametric statistical tests (t test for independent variables, statistical nonparametric tests - addressed to categorical variables ($\chi 2$ test of association, of the link between two categorical variables, with OR calculation, pentru2 test to compare two proportions), statistical nonparametric tests for ordinal data or addressed to numerical variables when the normality condition is not satisfied (Mann-Whitney U Test, Kruskal-Wallis Test), Kaplan-Meier Analysis.

17. Results

Statistical description of the patient group

Nervous system disorder		**Frequency**	**Percent**
	HAD	65	39.16
	CT	16	9.64
	PML	38	22.89
	PCL	4	2.41
	E.CMV	3	1.81
	E.HSV1,2	1	.60
	CrSNC	8	4.82
	AVC	12	7.23
	HIV SNP	11	6.63
	NCC	1	.60
	TBC SNC	7	4.22
	Total	166	100.00

Table 7: Neurological complications of HIV infection (HAD = HIV-associated dementia, CT = cerebral toxoplasmosis, PML = progressive multifocal leukoencephalopathy, PCL = primary cerebral lymphoma, E.CMV = cytomegalovirus encephalitis, E. HSV1,2 = herpes simplex encephalitis, CrSNC = cryptococcosis of the central nervous system, AVC = stroke, HIV SNP = neuromuscular complications of HIV infection, NCC = neurocysticercosis, TB SNC = tuberculosis of the central nervous system)

Between June 2012 and June 2020, 166 patients were identified as suffering from HIV-associated neurological complications.

Study of the three main neurological complications: HIV-associated dementia, progressive multifocal leukoencephalopathy, cerebral toxoplasmosis

Considering the frequency of the 3 mentioned diseases, I chose to highlight for each group, HIV-associated dementia, progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, if the onset of the disease is correlated with the risk factors followed, how each group is differentiated but also survival curve for each group, using the statistical methods described in the previous chapter.

The methodology of data collection, as well as their statistical processing is the one described above, with clarifications regarding the formation of the first batch, that of patients with HIV-associated dementia (HAD).

The group contains patients who, during the regular visit to the psychologist, had neurocognitive complaints consisting primarily of memory loss, psychomotor slowness or attention or concentration deficit [27].

If to one of the 3 questions, the patient answered "yes, sure", then the patient was evaluated in order to exclude comorbidities that occurred in the last 6 months, namely: opportunistic CNS infections, craniocerebral trauma, drug use, consumption chronic ethanol.

If the results were negative to the 4 questions addressed, then we proceeded to the screening tests, namely: the International HIV Dementia Scale (IHDS) [539], as well as the patient's self-assessment (PAOFI) [540].

Only patients who had results of no more than 10, including 10 on the IHDS scale, were selected in the group with HAD, the level of separation on the PAOFI scale being the score of 99, all patients who agreed to complete this questionnaire gave answers that totaled over 99 points.

The first 3 diagnoses in terms of frequency in the studied group were the same as those obtained in 2010, in Great Britain, except for the order of frequency. A higher frequency of CT versus PML was obtained in the British cohort. In our comparatively small group, PML was the second most common disease [542]. In a smaller study, which included only 60 patients with neurological conditions, conducted in China, the results are completely different. First by frequency is ranked cryptococcal meningitis with 22%, while in the studied group it represents only 4.82%. CT is on the second place with 17% higher percentage than in the studied group which is 9.64%, and CNS tuberculosis is on third place with 11.7%, above the value obtained in the study group which is 4.22%. [543].

The 2 groups of patients with whom the comparison was made are of very different sizes, with working methods that can generate differences, but most importantly, because we are talking mostly about opportunistic infections, we must take into account the geographical

epidemiological differences, Asia versus Europe. Thus, one can understand and anticipate the similarity or discrepancy with the studied group.

Compared to the total number of patients under monitoring and in treatment at the Constanța facility, the frequency of HAD would be approximately 6.5%, CT 1.6%, and PML 3.8%. Compared to 2.4% which was the frequency of HAD in the CHARTER study [25], the percentage is higher. But we must consider two aspects. The methodology described above for including patients in this category is based on screening testing, and not on complex neuropsychological tests by cognitive domains, being more estimative assessment of the degree of cognitive decline, even if its presence is certain. As a result, patients with MND may have been included in this category. The second aspect is that of the characteristics of these patients, most of them coming from the cohort of children who got the infection from their parents in Romania in 1987-1990, who already, at the time of including them in this study had had an HIV infection many years, long exposure to ARV treatment, which are components worthy of consideration, as they are risk factors for the development of cognitive decline.

The prevalence of PML 3.8%, falls in the range of 3-7% cited in the literature for the prevalence of PML before cART [191, 192], in correlation with the low compliance of these patients.

The percentage of 1.6% for CT is small, compared to the literature. Most patients have undergone multiple changes and suffer of many diseases, however, in the study we considered only the neurological disease whose onset took place during the proposed period. Many of the patients have a personal pathological history and cerebral toxoplasmosis, but being previously June 2012, they were not included in the analysis from this point of view. We can also interpret that, with cART, but also with the establishment of primary prophylaxis, the frequency is expected to be much lower. There are previous cART studies showing the occurrence of T. gondii encephalitis in 26-38% of toxoplasma seropositive AIDS patients 2 years after the diagnosis of AIDS [278, 279], as well as studies showing a halving of the frequency in the post-cART era [283, 284].

The average age at which patients in the group were diagnosed with HAD was 26 years, with CT 30 years, and PML 30 years. The age range corresponds to the best numerically represented age range nationally, 25-34 years [9]. For patients infected in childhood, another aspect to consider is that of the effect of the virus on a developing nervous system, perhaps in this context can be explained and associated HIV encephalopathy at a young age, which remains to be studied.

There was no significant difference between the main conditions, HAD, CT, PML in terms of patients' sex, the percentages being balanced between male and female for all 3 conditions.

Similarly, there were no significant differences related to the environment of origin, rural or urban, the percentages being evenly distributed in the 3 groups, patients with HAD, CT and PML, but also between the 3 groups.

By 2016, 95.38% of patients with HAD had been diagnosed. The predominant inclusion of patients in 2013 is due to the existing national screening project at that time which raised the issue of cognitive decline among HIV patients infected by parents in childhood [544]. Although the establishment of neurocognition screening tests is a controversial topic, the increased attention paid to the issue highlighted aspects of the daily functionality of these patients, their

poor social status and finally the negative influence of neurocognitive disorders on quality of life.

The annual distribution of cases of cerebral toxoplasmosis (CT) was much more balanced, remaining between 6.25% -12.5%, in most years, respectively 2013, 2014, 2016, 2018, 2019, 2020, with no patient in 2017, and only an insignificant increase in 2012 and 2015, respectively. Probably the primary prophylaxis of patients with CD4 <100 cells / mm3, but also the attempt to increase penetrability in the central nervous system, proved their effectiveness, in an attempt to decrease the frequency of this pathology.

Regarding the annual distribution of PML cases, this shows a relatively constant frequency from year to year, between 2012-2020, suggesting that PML, despite HAART and efforts to reduce morbidity and mortality from this condition, remains a dreaded complication of HIV infection.

Regarding the age at which patients were diagnosed with HIV, there is an average of 13 years of age in the HAD group, 21.5 years of age in the CT group and 17.92 years of age in the PML group. The studied group was mixed in terms of transmission, including patients from the cohort of children of HIV-infected parents in the years 1987-1990, which leads to a decrease in the average age at diagnosis of HIV infection.

By comparing patients who were HIV infected by their parents and other patients with another HIV transmission, there are significant differences in the frequency of parent transmission among those with HAD versus patients with CT or PML. There is a link between the two variables, “transmission pathway” and “type of neurological condition”: $\chi 2calc = 13,586$, $df = 2$, $p = 0.001 < \alpha = 0.05$ (Chi-Square Test). Discussions from this point of view must take into account the methodological limitations of recording patients with HAD (not requiring a diagnostic protocol applied over the years), but the possibility of a higher frequency of cognitive decline in patients infected by their parents in childhood should not be ruled out. This group of patients spent extended period in hospital, some were institutionalized, there were social and educational limitations that reduced their balanced development and functional integration not only into the structures of today's community, but also in everyday life [545].

The number of years from diagnosis of HIV infection to diagnosis of neurological complication ranged from 0 (diagnosis of neurological complication was inaugural diagnosis of HIV) to 24 years for patients with HAD, 20 years for patients with CT, 28 years for patients with PML. The average duration of HIV infection in the diagnosis of neurological disease was 13.03 for patients with HAD, 8.81 for those with CT and 12.58 for those with PML. Neurological complications such as HAD, CT or PML occur in advanced stages of the disease, being included in the list of AIDS defining diseases [546].

The mean and median values of the number of CD4 lymphocytes at the diagnosis of neurological complication were 539.14, respectively 523 for patients with HAD, 65, respectively 16 cells / mmc for patients with CT and 100.08, respectively 79.5 for patients with PML. Median CD4 values at diagnosis differ statistically significantly depending on the type of neurological condition: HAD with CT, HAD with PML ($p < 0.001$, Independent Sample Median Test). The reduced immune reserve mirrored by low values of CD4 at the diagnosis of neurological complication is directly correlated with the patient's vulnerability to opportunistic infections and has a lower correlation with the time of finding cognitive decline. Cognitive impairment, installed over time and documented at one time correlates with classic risk factors indicating disease severity, such as CD4 value at diagnosis, CD4 nadir value, long duration of HIV

infection, history of defining diseases for AIDS, viral load [55], but other risk factors are also very important, such as vascular and metabolic risk factors [60].

Since patients are receiving combination antiretroviral therapy, HIV-related cognitive decline is seen at higher CD4 levels, approaching normal [56]. The group with HAD had a significantly higher proportion of patients diagnosed at CD4 values ≥500 cells / mmc than the proportion of patients with CD4≥500 cells / mmc in the groups with CT or PML. The proportions of patients will vary inversely in the category with CD4 <200 cells / mmc, being higher in the groups with CT and PML, showing the association between the immunological imbalance and the susceptibility to opportunistic infections [547].

CD4 nadir (cells / mmc) had a mean value of 144.28 and a median of 70 in the group of patients with HAD, the mean value 133.13 and the median 23.5 for the group with CT, and in the group with PML the mean values of CD4 nadir was 68.71, and the median was 34. Thus, the median values of CD4 nadir do not differ significantly statistically, depending on the type of neurological disease ($p = 0.205 > 0.05$, Independent Sample Median Test), in the studied groups. The median CD4 nadir value was relatively low in all studied groups-70, 23.5 and 34. The correlation between low CD4 nadir values and the occurrence of cognitive decline was one of the conclusions of the CHARTER study. [55].

The proportion of patients with PML is statistically significantly higher ($p < 0.05$) in the CD4 nadir category below 100 cells / mmc, compared to the proportion of patients with HAD or CT in this category, showing a severely altered immune status even compared to patients with CT or HAD.

The median values of viral load were for patients with HAD 40 copies / ml-value that in the present study we considered the value from which the patient is undetectable- for patients with CT 34250 copies / ml and for patients with PML 125590 copies / ml.

Therefore, in the studied group, the patients with PML were the ones with the highest viral load, with statistically significant differences compared to those with HAD or CT, the worst therapeutic control being in the category of those with PML. One of the current problems is poor compliance to treatment in adults who have already been on chronic ARV treatment for more than 20 years. Because of this low compliance, whether we are talking about long-term survivors, those parent-infected in childhood, or whether we are talking about other categories of patients, despite the current immunologically effective treatment, disabling or fatal conditions such as PML still affect HIV-positive patients.

In the groups studied with HAD, CT, PML, no statistically significant differences were found generated by hepatitis B virus (HBV) co-infection.

HCV co-infection is found more frequently in groups with CT and PML and less in those with HAD. HCV appears to increase HIV-1 neurotoxicity [569]. HCV would have a negative impact on the recovery of CD4 lymphocyte counts, with cirrhosis being associated with low CD4 counts, regardless of HIV or HCV infection [570]. Given the interactions described, the exacerbation of HCV replication with decreasing CD4 lymphocyte counts, the correlation with CT and PML and less with HAD becomes understandable in the context of severe immunosuppression.

In the study group, co-infection with T. pallidum was more common in infected patients and with T. gondii. Both T. pallidum and T. gondii attach to host tissue through an extracellular matrix component, laminin, which is the major glycoprotein in the basal membrane. [579, 580] Probably a more frequent association of T. pallidum with T. gondii in HIV-positive patients, in

the case of the studied groups, are also explained by the fact that they have a similar pathogenic mechanism. The hypothesis requires further study in order to be proven.

Between the proportion of patients with HAD with TB and the proportion of patients with CT, PML with TB there are statistically significant differences ($p < 0.05$), in the studied group. HIV co-infection is the strongest known risk factor for progression from latent TB to active disease. Tuberculosis in an HIV-infected person accelerates the progression of HIV-related disease, probably through prolonged immune activation [585]. cART and the treatment of latent tuberculosis have been shown to significantly influence the incidence of TB in HIV-positive patients [586, 587]. Both TB and HIV infection are diseases that cause immunosuppression with a decrease in the number of CD4 cells [588] and probably with an increased risk of developing other opportunistic infections such as CT or PML.

There are statistically significant differences ($p < 0.05$) between the proportion of patients with HAD who had epileptic seizures and the proportion of patients with CT, PML who had epileptic seizures. Although seizures were also described in patients with HAD in the study group (4.6%), they were more common in patients in groups with CT (56.2%) or PML (50%). Moreover, in more severe cases of HAND, such as HAD, seizures have been described in 11% of cases [13]. Patients with known brain sequelae were excluded from the group with local HAD, many of whom had secondary epilepsy as a sequela. Epileptic seizures have been reported as one of the initial manifestations of cerebral toxoplasmosis in 15-40% of cases. [589, 590] and in patients with PML are cited in 20% of cases [205]. Patients with pre-existing epilepsy, alcohol or weaning drugs were not excluded from the CT and PML groups studied. Epilepsy was noted whenever it was reported in the diagnosis or in evolution.

Motor deficit was found on objective examination in 10 (62.5%) of patients with CT and in 28 (73.7%) of patients with PML. None of the patients with HAD had a motor deficit. As previously mentioned, patients with post-opportunistic cerebral sequelae or after craniocerebral trauma were excluded from the neurocognitive screening test.

Opportunistic focal infections, as expected, generate significant outbreak deficits and a high degree of disability, many of the survivors remaining with significant sequelae, which generally persist despite neurorehabilitation procedures.

In the study group, balance / coordination disorders were found, proportionally more significantly in patients with PML, probably through an earlier and more frequent impairment of the anatomical structures involved in maintaining these functions.

There are statistically significant differences between the proportion of patients with impaired consciousness in HAD versus the proportion with such changes in PML or CT ($p < 0.05$). Extensive PML lesions much more affect the general condition of patients and significantly influence the state of consciousness.

Most patients with HAD were diagnosed when they were undergoing ARV treatment, showing that the onset, in this case, is insidious, and the disease progresses in time, without direct connection with the therapeutic regimen at that time. In fact, the increased frequency of diagnosing cognitive decline, despite ARV treatment is a much-debated topic with various proposed explanations: either the existence of a previous neuronal injury [27], or a second wave of penetration at the CNS, the existence of the HIV reservoir in CNS [596, 597, 119], HIV-induced metabolic changes that increase cardiovascular risk factors and accelerate amyloid deposits, ARV inefficiency for CNS, and ARV neurotoxicity.

Of the 119 patients in the 3 groups - HAD, CT and PML - in 10 (8.4%) patients, the onset of neurological pathology led to the investigation and diagnosis of HIV infection, the neurological diagnosis thus becoming the inaugural diagnosis of HIV. There were no statistically significant differences between the 3 groups from this point of view. Given that all 3 conditions, HAD, CT, PML, fall into the category of conditions that define AIDS according to the Centers for Disease Control (CDC) [546], these patients with inaugural diagnosis are also late-presenters. Early initiation of ART is considered one of the most effective methods to reduce the risk of transmitting HIV, but early diagnosis of HIV is a challenge [599]. About half of HIV-positive patients are diagnosed late worldwide [600].

Most patients diagnosed with HIV had already followed 2 or 3 therapeutic regimens at the time of neurological diagnosis. Since the start of ARV treatment in the center of Constanța in 1996 to date, some of the patients, especially those in the cohort of infected children in the years 1987-1990, have gone through various therapeutic regimens, as new substances have entered use but also depending on their compliance and resistance to treatment. Patients with a large number of therapeutic changes are in the category of CT and PML being probably the least compliant, with a much impaired immune status and as a result at risk of opportunistic infections.

There are no statistically significant differences generated by the class of ARV drugs in the chronic treatment of patients in the 3 groups.

The CNS penetrability score of the last ARV scheme in which patients in the HAD group were found ranged from 0 to 13, with a mean of 8.08, a median of 8 and a module of 8. Penetrability score for patients with CT was between 0 and 13, mean of 6.56, median of 7.5 and module of 0. In patients with PML the penetrability score at the CNS was between 0 and 14, mean of 8.45, median of 9 and mode of 9. Although the values are high, i.e., the ARV scheme has a good penetrability in the CNS, the patients in the study continued to have neurological complications, such as HAD, CT or PML, the explanations being more.

On the one hand, compliance is obviously an important factor, on the other hand this scoring system has its limitations, such as didactic assignment of numerical value, does not take into account the possible damage to the blood-brain barrier or the toxicity of some drugs or drug interaction as well as a lack of clear methodology used in formulating this score.

Although the proportion of patients with HAD (n = 42, 64.6%) compliant with treatment is statistically significantly higher than the proportion of patients compliant with treatment with CT (n = 3.18.8%) or PML (n = 9.23, 7%), of the patients with HAD being 64.6% compliant with treatment, patients with cognitive decline continue to be the most numerous again raising the issue of increased prevalence of cognitive decline despite viral suppression.

In the 1990s, it was discovered that despite the combination of antiretroviral therapy (cART) increasing CD4 levels in most patients, some patients continued to develop HIV-associated neurocognitive disorder (HAND). Compared to other diseases that define AIDS, HAD (HIV-associated dementia or AIDS complex dementia as it was then called) had a higher frequency in the cART era [56]. The prevalence of all types of HAND remained similar in the pre- and post-cART era, at about 40% [93]. Even if there is good systemic control, HIV can remain active in the CNS sanctuary in some patients. Cerebral atrophy and neuroinflammation continued to be described on NMR spectroscopy despite cART [151]. The introduction of cART can lead to Immune Reconstitution Inflammatory Syndrome (IRIS), especially in those with low CD4 or those treated for opportunistic infections. On MRI scan, the volume of the affected white matter appears increased after CD4 recovery, suggesting the role of neuroinflammation [634]. It

can be interpreted that some patients do HAND despite cART for this reason, although it does not seem to explain the phenomenon enough. With better HIV screening and faster detection (at higher CD4 values) the risk of IRIS will be decreased. The fact that nonstructural proteins such as Tat have been shown to be neurotoxic, even in the absence of virion replication, is of great significance for treatment [635]. It shows that current cART schemes targeting viral replication are not enough.

Prior to antiretroviral use, the average life expectancy with HAD was 6 months, correlating with low CD4 cell counts [44]. With the introduction of cART there has been a noticeable improvement reaching an average of **40 months** [45, 46]. The mean survival time of the patients with HAD in the study was **87 months**, above the average specified in the literature, the therapeutic regimens being updated and improved towards a good CNS penetrability and optimized antiviral efficiency.

The median survival time in a cohort study of patients with PML and HIV increased from 0.4 to 1.8 years with the introduction of cART in some patients more than 10 years after diagnosis [176]. The median survival time in the present study of patients with PML was 5 months, within the quoted interval but leaving room for improvement.

Study of opportunistic infections versus other neurological complications

There are no statistically significant differences according to sex, age, origin, route of HIV transmission or duration of HIV infection between the group with opportunistic infections (IO), respectively the group with other neurological complications (ACN) i.e., HAD, stroke or HIV manifestations at the level PNS.

When we differentiate by age categories, a dependency relationship appears between the two variables "Age (years)" and "Group": $\chi 2calc = 10.986$, $df = 2$, $p = 0.004 < \alpha = 0.05$ (Chi-Square Test). There are significantly proportional more patients under the age of 30 in the group with other neurological complications (ACN) versus the proportion of patients under the age of 30 in the group with opportunistic infections (OI). However, the proportion of patients with OI aged between 30 and 50 years is significantly higher than the proportion of patients with ACN in the same age group. While in the age group over 50 years there are no significant differences between the proportions of patients related to each group of diseases.

Of the 78 patients in the ACN group, 65 (83.3%) were patients with HAD, who came mostly from the cohort of infected children in 1987-1990. The duration of HIV infection and exposure to ARV treatment in these patients is longer. Returning again to the topic of the persistence of high frequency of cognitive decline despite ARV treatment, it must be taken into account, in the studied group, that despite the young ages compared to the general population, the date of HIV infection is in the first years of life.

In the age category [30-50) years, OI predominates. Some patients are adults who have been infected since childhood and now, after many years of treatment, raise the issue of adherence to treatment, but also represents the age range that predominates among those with sexually transmitted HIV. According to national reports [9] 62% of patients became infected with HIV through heterosexual transmission and 24% in the category of men who have sex with men, a total of 86% of HIV infection transmitted sexually, and the age category with the most patients reported in 2019 it was between 25 and 34 years old.

In the group of patients with OI, a relatively homogeneous distribution of patients is noted, at the middle of the observed period, in 2016, 66.67% of the total number of patients being already registered. Even if they are years with lower percentages of frequency (2014, 2017) they are followed by years in which the OI frequency increases again (2015, 2018).

In the group with other neurological complications, by 2016, the middle of the period, 85.23% of patients were already registered. The distribution is balanced by years, except for 2013, when screening for cognitive decline was tested in the national project, several patients in the infected children cohort, therefore the diagnosis became more common. The national screening of the neurocognitive decline shed light on one of the problems faced by patients in the effort to integrate socially, but also raised the issue of the apparent effectiveness of the ARV scheme and the possibility of improving it as appropriate.

The value of CD4 lymphocytes at the diagnosis of neurological disease for patients with IO had an average of 124.82 and a median of 79.5, while in the ACN group the mean was 455.02 and the median 370. It is observed that the distribution of CD4 at diagnosis (cells / mmc) differs statistically significantly in patients with opportunistic infections compared to patients with other neurological complications ($p < 0.001 < 0.05$, Mann-Whitney U Test). The immune reserve correlates with patients' vulnerability to OI and is also a risk factor for HAD, stroke or neuromuscular complications. However, for this second category, included in the ACN group, there must be other mechanisms and other risk factors considered, such as accelerated atherosclerosis, premature aging, chronic inflammatory status, which are not discussed but whose value is clear in this context. Moreover, if we divide into categories according to the CD4 value at diagnosis, the results are even more obvious. The proportion of patients with OI with CD4 at diagnosis <200 cells / mmc is significantly higher than the proportion of patients with ACN with CD4 at diagnosis <200 cells / mmc ($p < 0.05$, Chi-Square Test for the comparison of two proportions). And the proportion of patients with AC4 with CD4≥500 cells / mmc is statistically significantly higher than the proportion of patients with OI with CD4≥500 cells / mmc.

Regarding CD4 nadir we can make similar observations. The mean value of CD4 nadir in the OI group was 89.06 and median 33, and in the ACN group it was 147.39 and median 89. Thus, the distribution of CD4 nadir (cells / mmc) differs statistically significantly in patients with opportunistic infections compared to patients with other neurological complications ($p < 0.009 < 0.05$, Mann-Whitney U Test). The differences are more obvious when we analyze according to the value category of CD4 nadir. The proportion of patients in the OI group with CD4 nadir <50 cells / mmc is significantly higher than the proportion of patients in the ACN group with CD4 nadir <50 cells / mmc ($p < 0.05$, Chi-Square Test for the comparison of two proportions). And, the proportion of patients in the ACN group with CD4 nadir≥100 cells / mmc is significantly higher than the proportion of patients in the OI group with CD4 nadir≥100 cells / mmc.

In the group with OI, the mean value of viral load was 565736.96, with a median of 92284, and in the group with ACN the mean viral level at the diagnosis of neurological disease 166859.01 with a median of 206. Thus, the distribution of ARN HIV differs statistically significantly at patients with opportunistic infections compared to patients with other neurological complications (HAD, stroke, HIV SNP) -$p < 0.001 < 0.05$, Mann-Whitney U Test. Therapeutic failure mirrored by the viral level in the diagnosis of neurological complication correlates with the occurrence of OI, less with the occurrence of HAD, stroke or complications in the PNS. In principle, no direct temporal correlation can be made with the onset of HAD, stroke

or HIV PNS, although the role of therapeutic efficacy is indisputable for the susceptibility to any neurological complication, probably with a different weight depending on the condition, taking into account a whole myriad of risk factors involved.

The risk of finding patients with HBV in the group with opportunistic infections is equal to the risk of finding patients with HBV in the group with other complications: OR (odds ratio) = 1,041; 95% IC = (0. 522, 2.076). The lack of impact of HBV co-infection on the immune and virologic response to ART on contracting AIDS-defining diseases or on HIV-related mortality [561, 562] explains the lack of differences between the two groups.

There are statistically significant differences between the proportion of patients with HCV coinfection in the IO group and the proportion of patients with HCV co-infection in the ACN group ($p < 0.05$, Chi-Square Test for the comparison of two proportions). HCV is known to have a negative impact on the recovery of CD4 lymphocyte counts [570], the predominant presence of OI in this context being explicable.

In the study group, only 6% of patients had HCV co-infection, a small percentage compared to the international prevalence that reaches 20% of HIV-HCV co-infected patients [563]. However, it should be borne in mind that the prevalence differs between risk groups, with the highest percentage being in the cohort of patients who abuse injecting drugs in the United States and Europe [564]. In Romania, in 2019, 10.8% of infected patients were included, depending on the route of HIV transmission, in the category of intravenous drug users [9].

The risk of finding patients with positive VDRL in the group with opportunistic infections is equal to the risk of finding patients with positive VDRL in the group with other neurological complications: OR (odds ratio) = 2,945; 95% IC = (0.555, 15.633).

In patients with OI, epileptic seizures and neurological outbreaks with a risk of creating disability and severely influencing daily functionality were much more common.

Of the 78 patients with OI, 51 (65.4%) had a motor deficit, and of the 88 patients in the ACN group, 15 (17%) had a motor deficit. Thus, of the 166 patients with neurological complications, 66 (39.8%) had a motor deficit at the objective neurological examination.

If we take into account the proportion of OI, 46.98%, in the general group of patients with neurological diseases, the percentage of 39.8% is a corresponding proportion, because even compared to the group of patients with neurological diseases, those with OI have a higher risk to present motor deficit.

The risk of finding patients with sensitivity disorder in the group with opportunistic infections is equal to the risk of finding patients with sensitivity disorder in the group with other neurological complications: OR (odds ratio) = 1.731; 95% IC = (0.785, 3.814). These results may be due to a reduced reporting of these disorders in the context of OI, when their detection may even be impossible in patients with altered general condition or aphasia, but also by associating these changes in patients with PNS disorders, thus the percentages are balanced.

There are statistically significant differences between the proportion of patients in group OI with cranial nerve damage and the proportion of patients in the ACN group with cranial nerve damage ($p < 0.05$, Chi-Square Test for the comparison of two proportions).

It should be noted that this category of cranial nerve damage was predominantly represented by cranial nerve paresis associated with focal lesions in OI, in the studied group no isolated cranial nerve paresis was reported. Thus, the risk will be similar to the risk encountered in the case of motor deficit. The same applies in the case of balance and coordination disorders.

There are statistically significant differences between the proportion of patients in the OI group with impaired consciousness and the proportion of patients in the ACN group with impaired consciousness ($p < 0.05$, Chi-Square Test for the comparison of two proportions).

The OI group, in fact, includes manifestations of these infections at the CNS level, often being associated with extensive lesions, sometimes even associating IRIS, this group of patients having a much deteriorated general condition correlated with the group of those suffering from diseases with predominantly slow progressive evolution (HAD, sensitive distal symmetrical polyneuropathy).

In the whole group, 16 (9.6%) of the patients were diagnosed with HIV infection following the diagnosis of the neurological condition. The percentage found in the literature of neurological disorders as an initial presentation of AIDS patients is 5-10%, CNS damage being found in 90% of cases at autopsy [645, 646]. The percentage found in the group from Constanța-9.6% is similar.

Of the 78 patients in the IO group, 61 (78.2%) received ARV treatment and 17 (21.8%) did not have ARV treatment at the time of diagnosis of the neurological complication. In the group of 88 patients with ACN, 77 (87.5%) had ARV treatment and 11 (12.5%) did not receive ARV treatment. Of all the 166 patients with neurological complications, 138 (83.1%) had ARV treatment and 28 (16.9%) did not receive ARV treatment at the time of diagnosis of the neurological condition.

Nationally, from the reports at the end of 2019 [9], out of a total of 16486 HIV-positive patients, ARV 13437 received treatment, i.e., 81.5% of patients. The patients in this study received therapy in a proportion of 83.1%, slightly above average and a significant percentage in value, as we refer only to patients with neurological disorders, demonstrating a good accessibility of treatment but also a persistence of neurological manifestations, despite the effort for appropriate treatment.

The chance of finding patients with INSTI in the group with opportunistic infections is 2,885 times higher than the chance of finding patients with INSTI in the group with other neurological complications: OR (odds ratio) = 2,885; 95% IC = (1,357, 6,130). The only side effects reported with medicines in this class were raltegravir, associated with psychosis, insomnia, nightmare [616] and elvitegravir, also associated with psychiatric side effects [617]. Given the small sample of patients undergoing this treatment, 26 of those with OI and 13 of those with ACN, it is difficult to make a clear correlation. Further studies are needed in this regard. Psychiatric disorders may influence treatment compliance and thus predispose to OI through therapeutic failure, rather than HAD, stroke, or peripheral neuropathy.

An important factor in the occurrence of neurological complications is compliance with treatment. In the group of patients with OI, 16 (20.5%) were compliant with treatment, 49 (55.7%) were compliant in the group with ACN and in the whole group, 65 (39.2%) patients were adherent to treatment. Thus, non-compliant patients were diagnosed proportionally more with IO versus ACN, so they have a higher risk of developing OI.

Among the patients studied, they reached the final event (death), 42 (53.8%) of 78, from the OI group and 11 (12.5%) of 88, from the ACN group. The risk of death is higher among patients with OI.

The mean survival time was 85.84 months for patients with other neurological complications and 44.74 months for patients with opportunistic infections. The median survival time for patients with opportunistic infections was 8 months. The estimated risk of reaching the

event of interest in patients with opportunistic infections is 5.9311 (= 1 / 0.1686) times higher than the estimated risk of reaching the event of interest in patients with other complications.

Death risk factors in patients with HIV-related neurological complications

In the group of patients who did not survive, 11 (6.6% of all patients) were co-infected with HBV and 6 (3.6%) were co-infected with HCV. There was no increase in the risk of reaching the final event, death, generated by co-infection with HBV or HCV.

The risk of reaching the final event (patient death) in the **ARV treatment** group is 2.53 times lower (1 / 0.394) than the risk of reaching the final event (patient death) in the group without ARV treatment: OR (odds ratio). risk / chance) = 0.394; 95% IC = (0.172, 0.902).

Low **compliance** ($p < 0.001 < \alpha = 0.05$) with treatment but also low CD4 upon diagnosis of neurological complication ($p < 0.001 < \alpha = 0.05$) increased the risk of death. In the group of patients who reached the final event, 39 (23.5% of 166) had CD4 <200 cells / mmc, 11 (6.6% of 166) had CD4 between [200-500) cells / mmc and 3 (1.8% of 166) had CD4≥500 cells / mmc.

In the group of patients who reached the final event (death), 28 (16.9%) had CD4 nadir <50 cells / mmc, 9 (5.4%) had CD4 nadir in the range [50-100) cells / mmc and 16 (9.6%) had CD4 nadir ≥100 cells / mmc. No influence on the risk of death was found.

In the group of patients who reached the final event (death), 29 (17.5% of 166) had the viral level <100,000 copies / ml and 24 (14.5% of 166) had the viral level≥100,000 copies / ml. In the group of patients who did not reach the final event (death), 81 (48.8% of 166) had the viral level <100,000 copies / ml, and 32 (19.3% of 166) had the viral level of 100,000 copies / ml.

The risk of reaching the final event (patient death) in the HIV RNA group (...- 100,000) is 2.09 times lower (1 / 0.477) than the risk of reaching the final event (patient death) in the HIV RNA group [100000 -...): OR (odds ratio) = 0.477; 95% IC = (0.242, 0.941).

In the group of patients who reached the final event (death), 24 (14.5% of 166) had epileptic seizures and 29 (17.5% of 166) did not have epileptic seizures. In the group of patients who did not reach the final event (death), 23 (13.9% of 166) had epileptic seizures and 90 (54.2% of 166) did not have epileptic seizures.

The risk of reaching the final event (patient death) in the group of patients with **epileptic seizures** is 3.23 times higher than the risk of reaching the final event (patient death) in the group of patients without epileptic seizures: OR (odds ratio or risk / chance ratio)) = 3,238; 95% IC = (1,594, 6,578).

18. General conclusions

Cognitive decline is the most common neurological complication associated with HIV, but it is necessary to standardize screening and diagnostic methods to be put into daily practice and achieve a common denominator between diagnostic and treatment centers. An important role at this stage is played by a psychologist who needs training for neurocognitive testing and whose presence in the multidisciplinary assessment and treatment team is absolutely necessary.

The persistence of HAD despite ARV, as well as the lack of a close correlation with traditional severity risk factors for HIV / AIDS, such as CD4 or viral levels, requires attention to the effectiveness of ARV therapy in the CNS, but also to cardiovascular risk factors in the context of HIV-induced metabolic changes, as well as on ARV-associated neurotoxicity.

Although the age is young, in these patients it would be appropriate to assess the neurovascular risk, by correlating the lipid profile with neurosonological and possibly neuroimaging results.

Although, currently, studies focus on the cognitive decline that continues to occur under effective ARV treatment, OI that significantly impacts the lives of patients are those that often require neurological examination and the correlation of clinical manifestations in the neurological area with neuroimaging. From the category of patients with cognitive decline, those who become chronic neurological patients are patients with HIV encephalopathy associated with secondary epileptic seizures that require chronic antiepileptic treatment. Antiepileptic treatment is another aspect that requires information from the treating neurologist, as HIV patients undergoing ARV treatment pose special and significant problems of multiple drug interactions.

The presence of the neurologist in the multidisciplinary team that should be formed for an evaluation and effective treatment of these patients is imperative, because, as we presented, the clinic, paraclinical and therapeutic regimen are different, compared to those found in immunocompetent patients.

19. Originality of the thesis

There are national studies that focus on neurocognitive decline and opportunistic infections, performed on groups of patients from the cohort of parent-infected children in 1987-1990. Not all neurological complications found in HIV-positive patients are addressed, regardless of the route of transmission, taking into account the parameters proposed by the present study, in none of the existing national or international studies. Through this study we highlighted the neurological complications in the entire group of patients registered with the Constanța facility, with the analysis of the impact of risk factors related to HIV / AIDS, the weight and risk attached to co-infection with various pathogens, with the presentation and analysis of neurological clinical manifestations as a necessary assessment for diagnosis and treatment, but also as a source of disability and mortality.

We also evaluated the effectiveness of ARV treatment by analyzing the main drug classes involved but also the CNS penetrability score and treatment compliance. Low adherence to treatment, statistically correlated with the risk of OI, is a topic that still needs to be addressed, as well as the percentage of late presentations, which still pose problems in achieving epidemiological control and eradication targets.

The comparative presentation of the main complications of HIV infection found in the study group was performed in order to assess where the susceptibility of these patients lies and how we can orient ourselves diagnostically and therapeutically. The differentiation of opportunistic infections versus other neurological complications comes after finding the high percentage of opportunistic infections with associated morbidity and mortality, but also in order to indirectly involve in the discussion other risk factors than the traditional ones associated with HIV infection. The study after reaching the final event shows the influence of risk factors indicating the severity of HIV / AIDS and epilepsy on mortality.

The HIV / AIDS epidemic is still ongoing, although more than 30 years have passed since the discovery of the virus, and also the description of the first neurological complications associated with HIV infection. Once we move away from the first cases and the first descriptions of pathology, the image becomes clearer but also much more complex with variables that, as they appear, try to transform them from unknown to known. Focusing on the neurological

complications of HIV infection in patients monitored by Constanța facility is a new approach, which aims to have good knowledge and understanding, opening further topics for discussion, proposing a special focus on investigative methods, but above all, transforming the numbers and percentages into methods to facilitate life improvement.

KEYWORDS: HIV infection, neurological complications, risk factors, survival

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