“OVIDIUS” UNIVERSITY OF CONSTANȚA
MEDICINE PH. D. SCHOOL
MEDICINE DOMAINE

Cerebral toxoplasmosis on immunodepressed HIV-infected pacients

PhD Thesis Summary

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Constanța

2024

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Abbreviations used in text

HIV- human immunodeficiency virus
DNA- deoxyribonucleic acid
CT- computer tomography
MRI- Magnetic resonance imaging
T+BD- multiple brain disorders including cerebral toxoplasmosis
T-BD- cerebral toxoplasmosis without other brain disorders
ADS- AIDS- dementia complex(AIDS encephalopathy)
PML- Progressive multifocal leukoencephalopathy
M-TBC- Tuberculous meningitis
M-NM- Meningitis with Neisseria Meningitidis
AVM- arteriovenous malformation
PNCSL- Primary central nervous system lymphoma
PRN- Polyradiculoneuritis
PFC- Central facial palsy
Dg- diagnosis
TMP-SMX- Trimethoprim- sulfamethoxazole
OR- Odds ratio
IC- confidence interval
HR- Harzard rațio
TBC- tuberculosis

General data about Toxoplasmosis

Toxoplasmosis represents one of the most widespread parasites worldwide. It is estimated that more than a third of the world's population has been infected with this parasite. Toxoplasmosis of the central nervous system affects 40% of HIV infected patients in the absence of antiretroviral treatment and is the most common opportunistic infection causing focal brain lesions.[1,2,3]

Three different neurological patterns are noticeable in central nervous system toxoplasmosis: diffuse encephalitis with or without epileptic seizures, meningoencephalitis, single or multiple abscesses-appearance of an expanding cerebral mass. The clinical onset is either subacute with focal neurological signs in 60-90% of cases related directly to the anatomical localization of the lesions, or acute, with focal or generalized epileptic tonic-clonic seizures (15-25% of cases).[2,3,4,5,6] More than 80% of those who develop cerebral toxoplasmosis have CD4 lymphocyte levels count below 100 cells/mm^3. [2, 4]

It is a probable risk factor for schizophrenia by increasing the brain dopamine concentration in the infected patients.[5,6,7]

The diagnosis is based on clinical and radiological findings, confirmed by serological tests such as ELISA or immunofluorescence antibody test and/or DNA T. Gondii detection by molecular methods.[8, 9,10,11]

The neuroimaging evaluation is performed by computer tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancing, with a role in establishing the diagnosis and monitoring the response to treatment.[12]

Lumbar puncture, when it can be performed helps to establish the diagnosis and displays lymphocytic pleocytosis, increased proteinorahia, normal or low glycorahia.[5,6]

It is **brain biopsy** that provides conclusive diagnosis. It is performed in certain situations: persistence or worsening of brain lesions under empirical anti-toxoplasma treatment, solitary brain lesion or atypical lesions on MRI or negative anti-toxoplasma serology.[6,12]

Histopathologic examination shows nonspecific changes: of lymphocytic meningitis, lesions containing cysts, astroglial and microglial nodules, associated lymphocytic vasculitis changes.[6]

The research interest on cerebral toxoplasmosis in HIV infected patients was aroused due to the fact is the most common cause of focal brain lesions in these patients and its association with other cerebral conditions, also occurring in HIV infection, is a topic that has not been extensively researched. Is representing one of the few diseases that benefit from curative treatment. In this research we compared patients who suffered from cerebral toxoplasmosis to those who suffered from several brain disorders in association with cerebral toxoplasmosis in terms of clinical manifestations, diagnosis, the impact of treatment on the evolution and prognosis, of mortality and morbidity. The studies on the impact of cerebral toxoplasmosis on brain functionality are few, so we performed 3-hour electroencephalography on convalescent or recovered patients.

Personal contribution

The study was conducted according to an analytical, observational, retrospective and prospective, case-control type model on patients diagnosed with cerebral toxoplasmosis and HIV from data base of the Regional Clinical Center and Constanta Infectious Diseases Clinical Hospital.

General methodology

Follow-up files from 1834 patients from data base of Constanta Infectious Diseases Clinical Hospital and the Regional Clinical Center for monitoring and follow-up HIV disease were investigated of which, 1039 patients were in active follow-up and 795 were archived files.

We enrolled in the study 94 patients HIV infected with cerebral toxoplasmosis until 01.12.2023. The data were extracted from the follow-up and record sheets at the Regional Clinical Center for HIV patients treatment as well as from the patients filles hospitalised in the HIV Department of the Infectious Diseases Clinical Hospital of Constanța.

Inclusion criteria:

- HIV infected patients who were diagnosed with cerebral toxoplasmosis or patients who were diagnosed with cerebral toxoplasmosis and HIV in the same time.
- Patients diagnosed with cerebral toxoplasmosis with CD4 lymphocytes level account determination at toxoplasmosis diagnosis establishment and after completed combined treatment.
- Patients diagnosed with cerebral toxoplasmosis with Ig G and Ig M anti-toxoplasma antibody account determinations performed

Exclusion criteria:

- Patients diagnosed with cerebral toxoplasmosis without CD4 account level determinations after completed cerebral toxoplasmosis treatment.
- Patients with cerebral toxoplasmosis suspicion without confirmation by serological tests, anti-toxoplasma antibodies titer Ig G, Ig M, without performed lumbar puncture or biopsy to confirm the diagnosis or who presented uncertain imaging findings.

Material and method

From the Database of Constanta Infectious Diseases Clinical Hospital and the Regional Clinical Center for Day Care for monitoring and treatment of HIV Patients, 1834 follow-up filles were analyzed from which 94 patients diagnosed with HIV and cerebral toxoplasmosis were enrolled in the study until 01.12.2023.

The 94 patients group was divided into two groups: one (T+BD) with 60 patients with cerebral toxoplasmosis associated with other brain disorders and the other (T-BD), including 34

patients with only cerebral toxoplasmosis. The two groups were comparatively analyzed in terms of neurological symptoms onset, diagnosis, clinical evolution after treatment initiation and cure/survival rate. An individual follow-up sheet was established for each patient included in the study, that contained a number of parameters that constituted the Research Database.

Statistical methods used

The data obtained were analyzed using IBM SPSS Statistics 25 statistical processing program. The procedures applied were: descriptive statistics (for the characterization of categorical and continuous variables defined on the database), graphs, parametric statistical tests: the t-test for independent variables, non-parametric statistical tests: the $\chi 2$ test of the association between two categorical variables, with determination of the risk- odds ratio OR, in certain situations, the z test for comparing two proportions, the Mann-Whitney *U* test (used to test the difference between two independent groups), Wilcoxon test (used to test the difference between two dependent groups), Kaplan-Meier survival analysis. Testing for normality was done with the Shapiro-Wilk test. In all situations, the level of significance chosen was $\alpha = 0.05$. [13,14,15]

Group Subdivision

		Frequency	Percent
Valid	T+BD	60	63.83
	T-AB	34	36.17
	Total	94	100.00

Table 1 Frequency and percentage of patients with multiple brain disorders including cerebral toxoplasmosis(T+BD) and those with cerebral toxoplasmosis(T-AC)

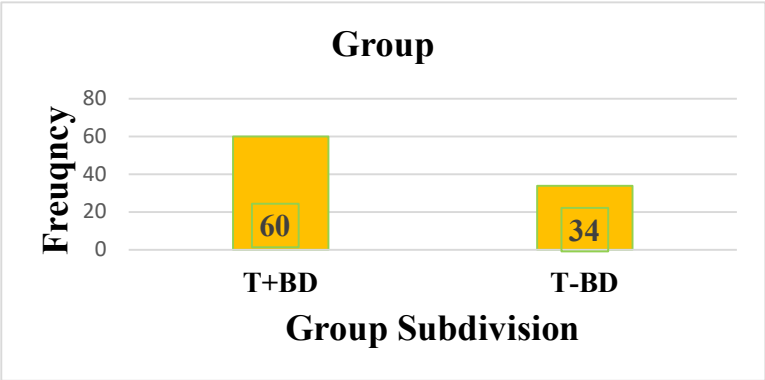

Fig. I Bar graph representation of the group variable T+BD/T-BD

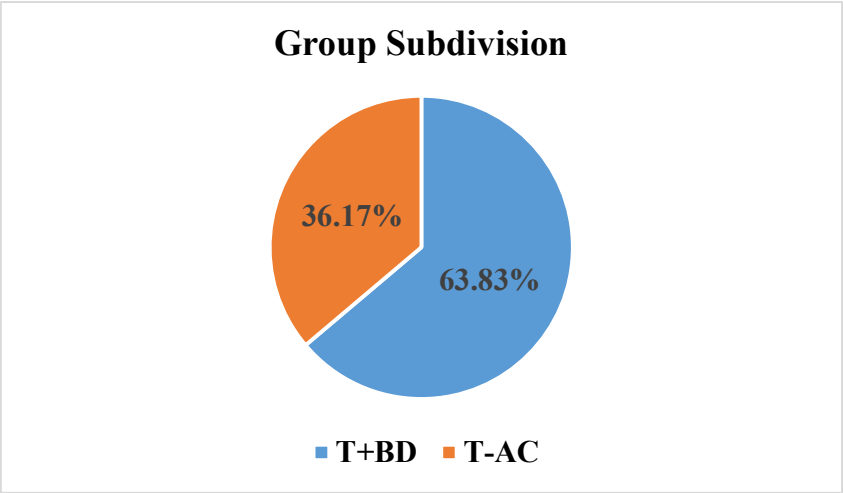

Fig. II Pie graph representation for the group variable.

Study results

1. Types of cerebral disorders associated with cerebral Toxoplasmosis in the studied group

		Frequency	Percent
T+BD	ADC	35	37.23
	LEMP	6	6.38
	M-TBC	4	4.26
	M-NM	4	4.26
	Stroke	6	6.38
	AVM	2	2.13
	PCNSL	1	1.06
	PRN	2	2.13
T-BD		34	36.17
Total		94	100.00

Table 2 Representation of the brain disorders types associated with cerebral Toxoplasmosis and the related percentages of their frequency occurence

2. Initial stage of HIV disease in the studied group

			HIV disease stage at diagnosis			
			A	B	C	Total
Lot	T+BD	Count	5	20	35	60
		% within Lot	8.33%	33.33%	58.33%	100.00%
	T-BD	Count	2	14	18	34
		% within Lot	5.88%	41.18%	52.94%	100.00%
Total		Count	7	34	53	94
		% within Lot	7.45%	36.17%	56.38%	100.00%

Table 3 Percentage representation of the studied groups T+BD/T-BD regarding the initial stage of HIV disease

There is no association relation between the variables Stage of HIV disease at diagnosis and group: $\chi 2calc = 0.656$, $df = 2$, $p = 0.720 > \alpha = 0.05$ at $\chi 2$ test of association between two categorical variables.

3. Other forms of toxoplasmosis in the studied group

			Other toxoplasmosis forms			
			Ocular	Lymphatic	No other localisation	Total
Lot	T+BD	Count	2	1	57	60
		% within Lot	3.33%	1.67%	95.00%	100.00%
	T-BD	Count	1	0	33	34
		% within Lot	2.94%	0.00%	97.06%	100.00%
Total		Count	3	1	90	94
		% within Lot	3.19%	1.06%	95.74%	100.00%

Tabel 4 Percentual representation of other toxoplasmosis forms in studied group T+BD/T-BD

The proportion of patients with other toxoplasmosis forms in the T+BD group (5.00%) does not differ significantly from the proportion of patients with other toxoplasmosis forms in the T-BD group (2.94%): $\chi 2calc = 0.003$, $df = 1$, $p = 0.955$ at test $\chi 2$ for comparing two proportions.

4. Associated neuropathies

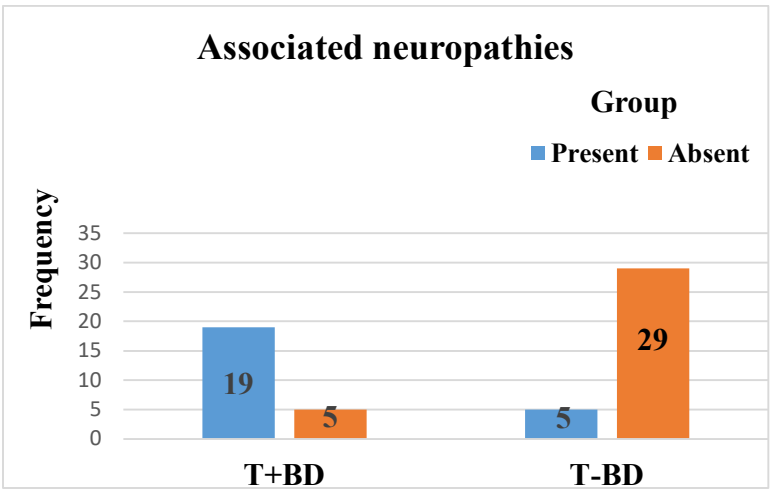

Fig. III Bar graph representation of associated neuropathies on studied groups T+BD/T-BD

The proportion of patients with associated neuropathies in the T+BD group (31.67%) does not differ significantly from the proportion of patients with associated neuropathies in the T-BD group (14.71%) according to the $\chi 2$ test for the comparison of two proportions: $\chi 2calc = 2.452$, $df = 1$, $p = 0.117$.

5. Clinical manifestations in the studied group

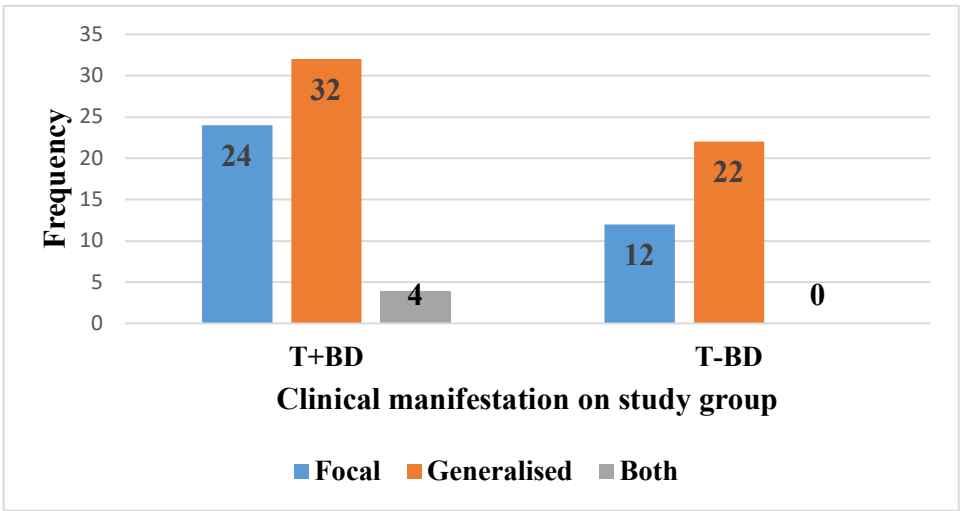

Fig. IV Bar graph representation of the presence of clinical manifestations on the T+BD/T-BD studied groups

6. Generalized tonic-clonic epileptic seizures in the studied group

			Generalized	Absent	Total
Lot	T+BD	Count	11	49	60
		% within Lot	18.33%	81.67%	100.00%
	T-BD	Count	1	33	34
		% within Lot	2.10%	97.90%	100.00%
Total		Count	12	82	94
		% within Lot	12.77%	87.23%	100.00%

Table 5 Percentage representation of generalized tonic-clonic epileptic seizures in studied groups T+BD/T-BD

The proportion of patients with generalized tonic-clonic epileptic seizures in the T+BD group (18.33%) differs significantly from the proportion of patients with generalized tonic-clonic epileptic seizures (TC) in the T-BD group (2.94%): $\chi 2calc = 3.859$, $df = 1$, $p = 0.048$ ($\chi 2$ test for comparing two proportions).

The risk of generalized tonic-clonic epileptic seizures onset in the T+BD group is 7.4 times higher than in the T-BD group (risk ratio OR = 7.408); 95% confidence interval (CI) for OR = (1,100, 60,144).

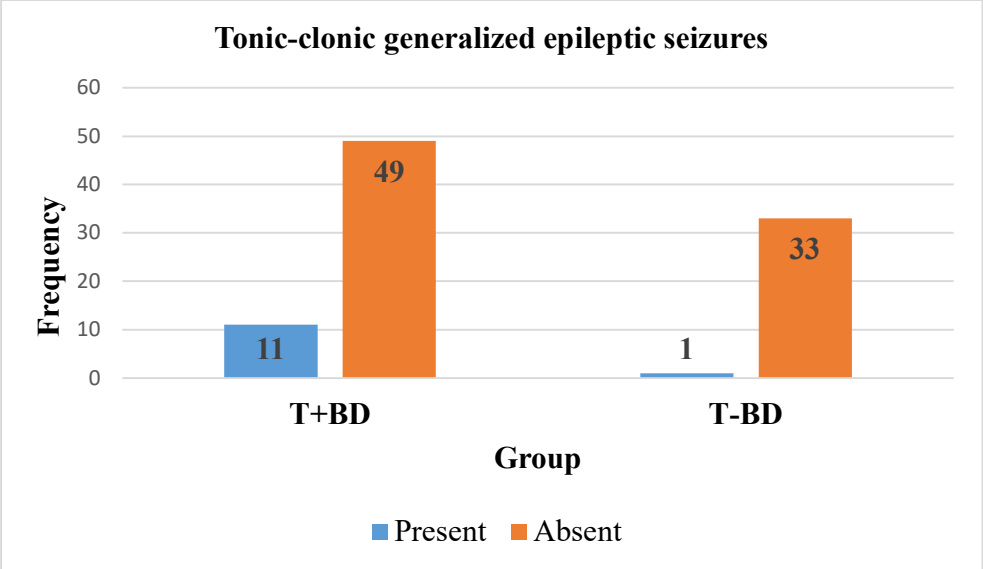

Fig. V Bar graph representation of the presence of generalized tonic-clonic seizures in the T+BD/T-BD studied groups.

7. Epileptic seizures with focal onset in studies group

At the $\chi 2$ test for the comparison of two proportions, the proportion of patients presenting focal epileptic seizures in the T+BD group (5.00%) does not differ significantly from the proportion of patients presenting focal epileptic seizures in the T-BD group (2.94%) as shown by $\chi 2calc = 0.003$, $df = 1$, $p = 0.955$ with a risk ratio $OR = 1.737$ is considered not significantly different from the value 1 (equal risk); 95% Confidence Interval (CI) for OR = (0.174, 17.383).

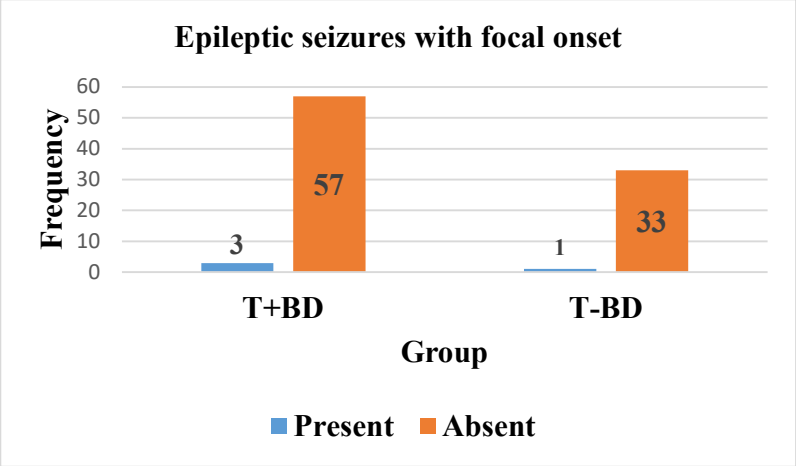

Fig. VI Bar graph representation of the presence of focal epileptic seizures on the T+BD/T-BD studied groups.

8. Motor deficit in the studied group

The risk of finding a patient with motor deficit in the T+BD patient group is equal to the risk of finding a patient with motor deficit in the T-BD patient group: the odds ratio OR = 1.506 is considered not significantly different from the value 1(equal risk); 95% confidence interval (CI) for OR = (0.576, 3.938).

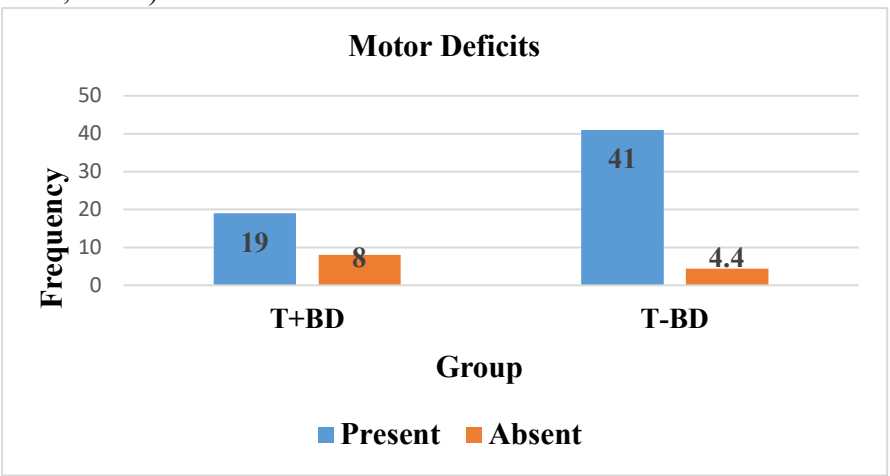

Fig. VII Bar graph representation of the presence of motor deficit on the T+BD/T-BD studied groups.

Subdivision of motor deficit types in the studied group

		Group			
		T+BD		T-BD	
		Count	% within Lot	Count	% within Lot
Motor deficits	Right/left hemiparesis	12	20.00%	5	14.71%
	Brahial paresis	3	5.00%	1	2.94%
	Crural paresis	1	1.67%	0	0.00%
	Paraparesis	2	3.33%	1	2.94%
	Central facial palsy	1	1.67%	1	2.94%
	Absent	41	68.33%	26	76.47%
Total		60	100.00%	34	100.00%

Table 6 The percentage representation of motor deficit types on the T+BD/ T-BD studied groups

9. Speech impairment in the studied group

The proportion of patients with speech impairment in the T+BD group (3.33%) does not differ significantly from the proportion of patients with speech impairment in the T-BD group (5.88%): $\chi 2calc = 0.003$, $df = 1$, $p = 0.954$ at the test $\chi 2$ for comparing two proportions.

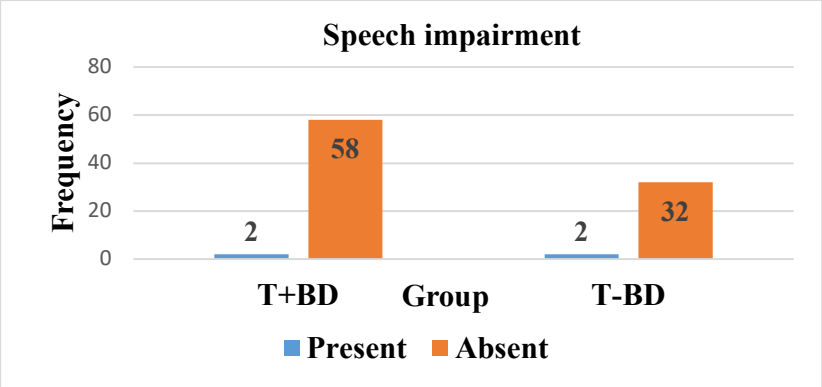

Fig. VIII Bar graph representation of the presence of speech impairment on the T+BD/T-BD studied groups.

10. Cranial nerve palsy in the studied group

The risk of finding a patient with cranial nerve palsy in the T+BD patient group is equal to the risk of finding a patient with cranial nerve palsy in the T-BD patient group: hazard ratio

OR = 3,000 is considered not significantly different of the value 1 (equal risk); 95% confidence interval (CI) for OR = (0.336, 26.805).

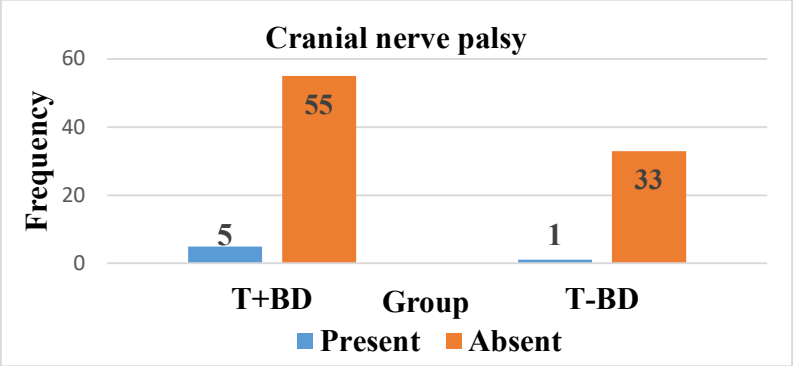

Fig. IX Bar graph representation of cranial nerve palsy on the T+BD/T-BD studied groups.

Subdivision of types of cranial nerve palsy

		T+BD		T-BD	
		Count	% within Lot	Count	% within Lot
Cranial nerve palsy	n.III	1	1.67%	1	2.94%
	n.III,IV,VI,IX,X	1	1.67%	0	0.00%
	n.VII	3	5.00%	0	0.00%
	Absent	55	91.67%	33	97.06%
Total		60	100.00%	34	100.00%

Table 7 Percentage representation of cranial nerve palsy in the T+BD/T-BD studied groups

11. Visual impairment in the studied group

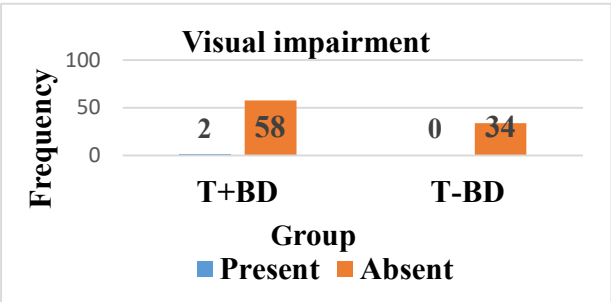

Fig. X Bar graph representation of visual impairment on T+BD/T-BD groups

Patients with visual impairment are represented in the T+BD group (3.33%) and in the T-BD group there are no patients with visual impairment (0.00%). In the $\chi 2$ test for the comparison of two proportions, the two groups do not differ significantly: $\chi 2calc = 0.110$, $df = 1$, $p = 0.740$.

12. Sensitivity impairment in the studied group

The proportion of patients with sensitivity impaiment in the T+BD group (8.33%) does not differ significantly from the proportion of patients with sensitivity disorders in the T-BD group (11.76%): $\chi 2calc = 0.031$, $df = 1$, $p = 0.858$ at the test $\chi 2$ for comparing two proportions.

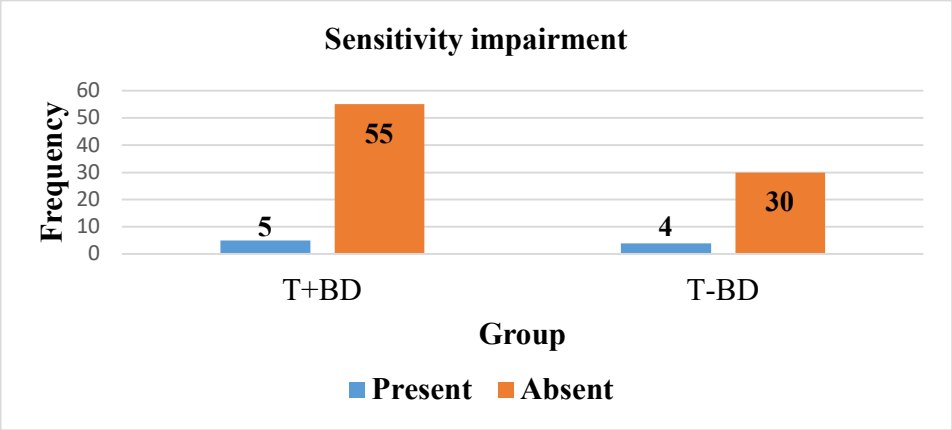

Fig. XI Bar graph representation of the presence of sensitivity impairment on the T+BD/T-BD studied groups

13. Gait and coordination impairment on the studied group

At the $\chi 2$ test for comparison of two proportions, the proportion of patients with gait and coordination impairment in the T+BD group (16.67%) does not differ significantly from the proportion of patients with gait and coordination impairment in the T-BD group (8.82%): $\chi 2calc = 0.560$, $df = 1$, $p = 0.454$.

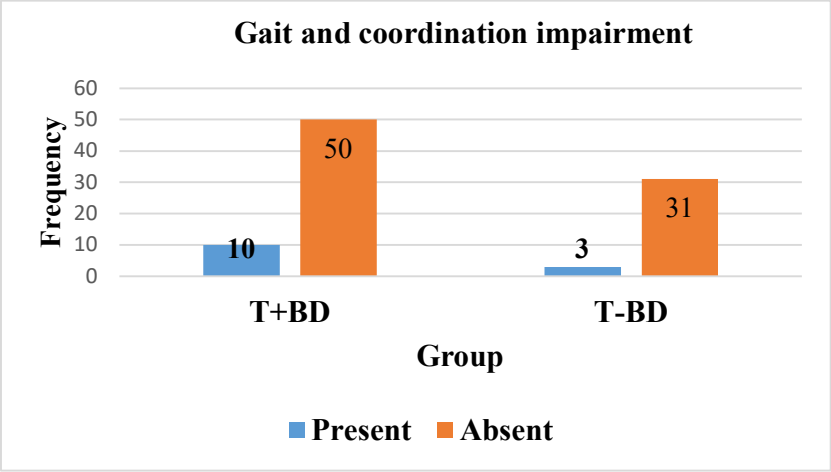

Fig. XII Bar graph of gait and coordination impairment on T+BD/T-BD studied groups.

14. Involuntary movements in the studied group

The proportion of patients with involuntary movements in the T+BD group (3.33%) did not differ significantly from the proportion of patients with involuntary movements in the T-BD group (0.00%): χ^2calc = 0.110, df = 1, p = 0.740 at the χ^2 test for the comparison of two proportions.

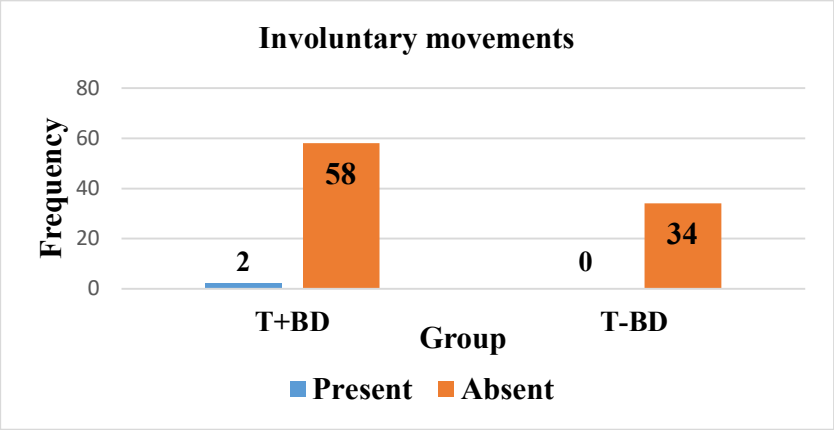

Fig. XIII Bar graph representation of the presence of involuntary movements on the T+BD/T-BD groups

Types of involuntary movements in our studied group

		T+BD		T-BD	
		Count	% within Lot	Count	% within Lot
Involuntary movements	Hemibalism	1	1.67%	0	0.00%
	Chorea	1	1.67%	0	0.00%
	Absent	58	96.67%	34	100.00%
Total		60	100.00%	34	100.00%

Table 8 Percentage representation of involuntary movements types in the T+BD/T-BD studied groups

15. Associated comorbidities

The proportion of patients with comorbidities in the T+BD group (66.67%) did not differ significantly from the proportion of patients with comorbidities in the T-BD group (47.06%): χ^2calc = 2.699, df = 1, p = 0.100 at the χ^2 test for two proportions comparison.

The risk of finding a patient with existent comorbidities in the T+BD group is equal to the risk of finding a patient with comorbidities in the T-BD group: the OR risk = 2.250 is considered not significantly different from 1 (equal risk) value; confidence interval (CI) 95% for OR = (0.951, 5.323).

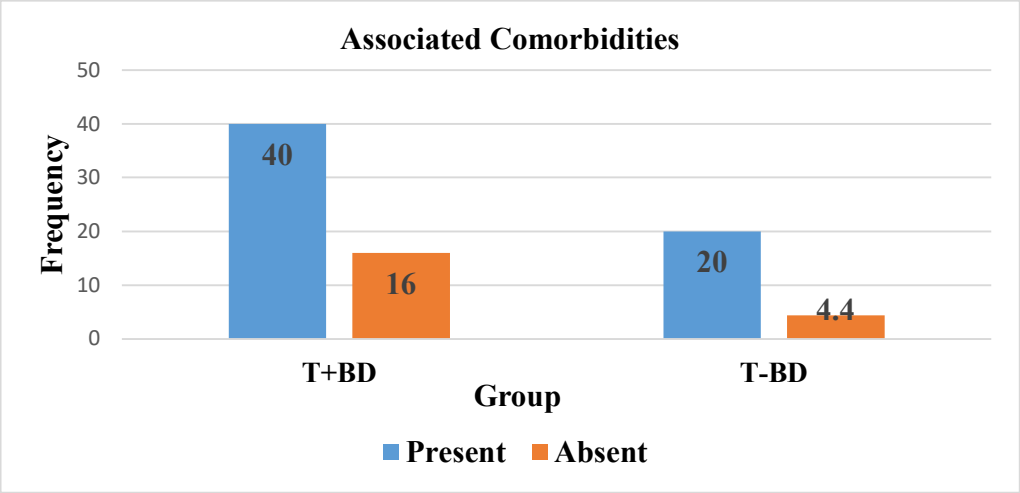

Fig. XIV Bar graph representation of comorbidities presence on studied groups T+BD/T-BD

16. CD4 count level at cerebral Toxoplasmosis diagnosis and CD4 count level after combined treatment (antitoxoplasma and antiretroviral)

Wilcoxon Signed Rank Test showed differences between median CD4 count level at cerebral toxoplasmosis diagnosis(cell/uL) and CD4 count level after treatment (cell/uL) in the T+BD group: $z = -3.863$, Mean(-) Rank = 20.6, Mean(+) Rank = 30.78, $p < 0.001$. For the T-BD group the test pointed out differences between median CD4 count level before combined treatment (cell/uL) and CD4 count level after combined treatment (cell/uL): $z = -3.616$, Mean (-) Rank = 9.07, Mean(+) Rank = 18.02, $p < 0.001$.

In both groups the CD4 lymphocytes count level is higher at the end of treatment compared to the CD4 count level at the establisment of Cerebral Toxoplasmosis diagnosis.

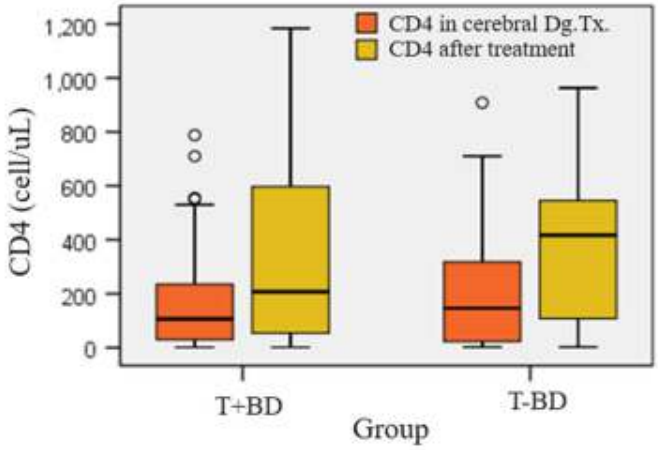

Fig. XV Box-plot graphic representation: CD4 at cerebral Dg.Tx. (cell/uL) and CD4 after treatment (cell/uL) in T+BD/T-BD studied groups.

17. Viremia level at cerebral Toxoplasmosis diagnosis and viremia level after combined treatment

For the T+BD group the test displayed a difference between the median level of Viremia (Log) at cerebral Toxoplasmosis diagnosis- Dg. (copies/mL) and the level of Viremia(Log) after treatment (copies/mL): z = - 2.747, Mean(-) Rank = 22.95, Mean(+) Rank = 16.81, p = 0.006. The post-treatment viremia level is decreased compared to cerebral Toxoplasmosis diagnosis Dg. (copies/mL).

For the T-BD group the test pointed out a difference between the median levels of Viremia(Log) at cerebral Toxoplasmosis diagnosis- Dg. (copies/mL) and the median levels of Viremia(Log) after treatment (copies/mL): z =- 3.826, Mean(-) Rank = 16.13, Mean(+) Rank = 7.00, p < 0.001. Viremia levels at the end of antitoxoplasma and antiretroviral treatment is decreased towards the begining of treatment.

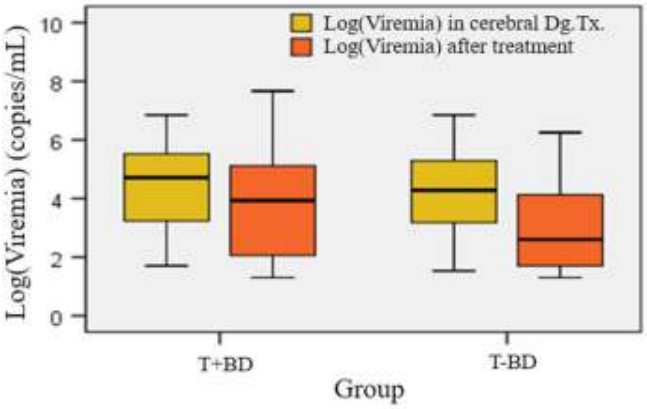

Fig XVI Box-Plot graph representation: Log(Viremia) at Cerebral Toxoplasmosis Dg. (copies/mL), Log(Viremia) after treatment (copies/mL) in T+BD/T-BD studied groups.

18. Mean life average from establishing cerebral Toxoplasmosis diagnosis until death

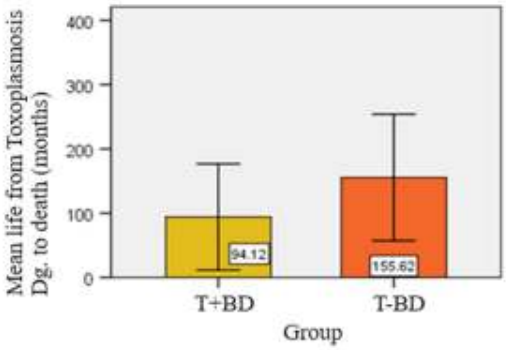

Fig. XVII Bar-Error graph representation for the variables Life span from Cerebral toxoplasmosis Dg. to death (months) in T+BD/T-BD studied groups.

There is a significant difference between the mean life values of Tx. Dg. until death (months) of patients in the T+BD group (94.12 months) compared to mean life patients from the T-BD group (155.62 months): t = -3.233, df =92, p = 0.002 at Independent Samples t-test.

19. The performed treatment on the studied group

			TMP-SMX	Clindamycin	Azithromycin	Pyrimetamine	Total
Lot	T+BD	Count	33	3	8	16	60
		% within Lot	55.00%	5.00%	13.33%	26.67%	100.00%
	T-BD	Count	20	0	6	8	34
		% within Lot	58.82%	0.00%	17.65%	23.53%	100.00%
Total		Count	53	3	14	24	94
		% within Lot	56.38%	3.19%	14.89%	25.53%	100.00%

Table 9 Percentage representation of administered drugs per studied group T+BD/T-BD

More than half of the patients in the group received treatment with Trimethoprim-sulfamethoxazole, about 1/4 received treatment with Pyrimetamine, both representing the first line treatment for cerebral toxoplasmosis. Azithromycin (14.89%) and Clindamycin(3.19%) were used less frequently, as they represents a second line medication.

20. Evolution under treatment of the studied group

The proportion of patients with unfavourable outcome in the T+BD group (56.67%) differed significantly from the proportion of patients with unfavourable outcome in the T-BD group (26.47%): χ^2calc = 6.805, df = 1, p = 0.009 at the χ^2 test for comparison of two proportions. The rate of poor outcome is 3.6 times higher in the T+BD group than in the T-BD group according to risk ratio OR = 3.632; confidence interval (CI) for OR = (l .452, 9.089).

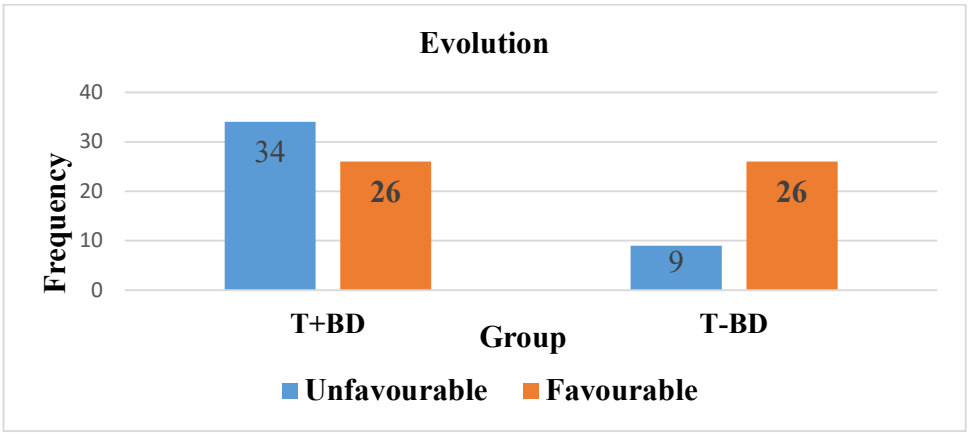

Fig. XVIII Bar graph of disease evolution in the T+BD/T-BD studied groups

21. Antiretroviral therapy adherence in the studied group

The proportion of patients with cART adherence in the T+BD group (43.33%) is significantly different from the proportion of patients with cART adherence in the T-BD group (75.53%): χ^2calc = 7.836, df = l, p = 0.005 (χ^2 Test for comparison of two proportions).

The cART adherence rate in the T+BD patient group is 3.636 times lower than in the T-BD patient group due to OR risk ratio = 0.275 is considered to differ significantly from 1 (equal risk); 95% confidence interval (CI) for OR = (0.110, 0.689).

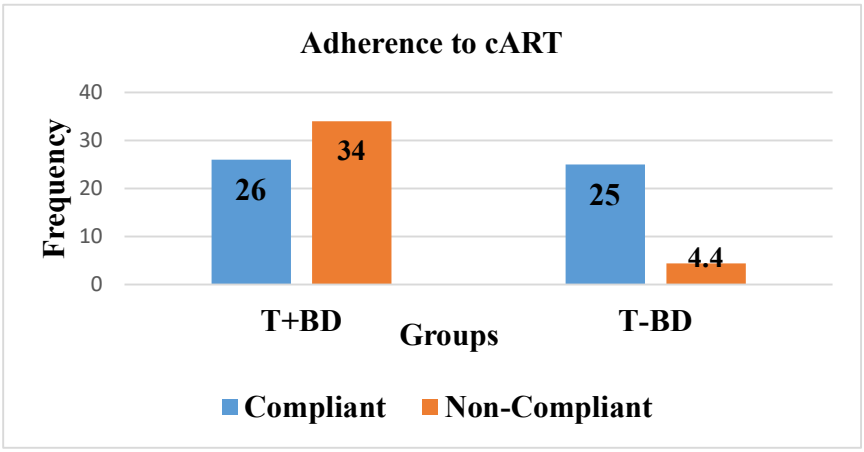

Fig. XIX Bar graph of cART adherence on studied groups T+BD/T-BD.

22. Survival after cerebral toxoplasmosis in the studied group

The proportion of patients who died in the T+BD group (78.33%) differed significantly from the proportion of patients who died in the T-BD group (50.00%): χ^2 calc= 6.765, df = 1, p = 0.009 at the test for two proportions comparison. The death rate in the T+BD group is 3.615 times higher than in the T-BD group. OR Risk ratio = 3.615 is considered to differ significantly from 1 (equal risk); 95% confidence interval (CI) for OR = (1.454, 8.987). An association is observed between the variables Survival after Toxoplasmosis and Group: χ^2calc = 8.018, df = l, p = 0.005 < α = 0.05 (χ^2 Test of association between two categorical variables).

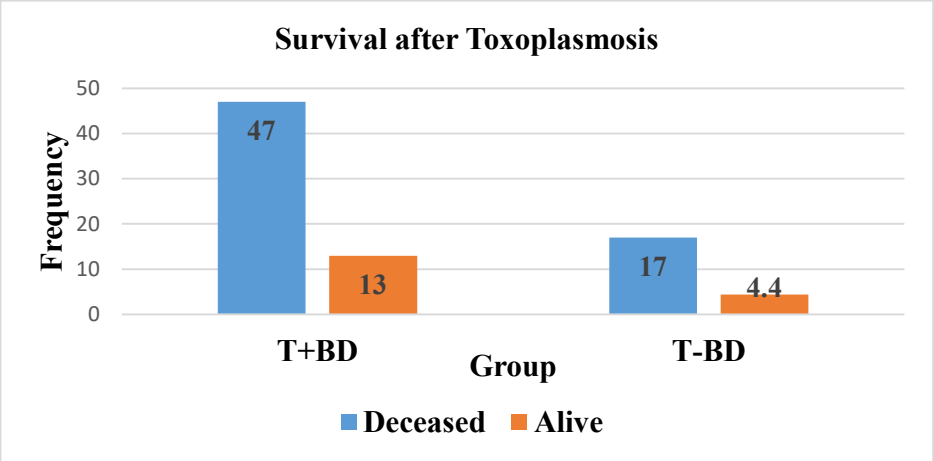

Fig. XX Bar graph of deaths on studied groups T+BD/T-BD

23. Kaplan-Meier survival curve

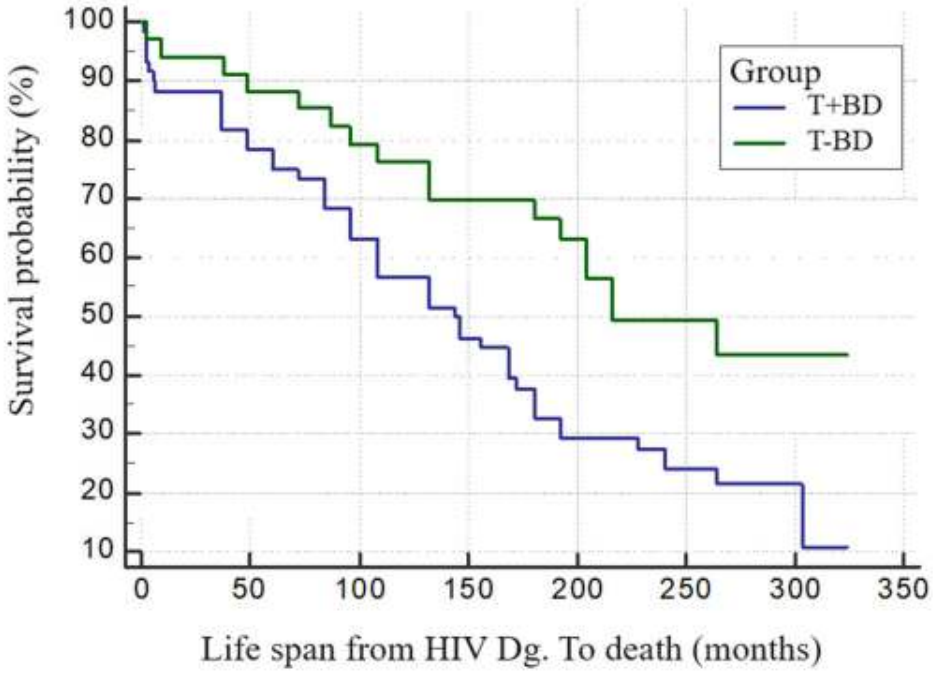

Fig. XXI Kaplan-Meier survival curve on studied groups T+BD/T-BD

The two survival curves differ significantly: Chi-square = 6.8592, df = 1, p = 0.0088 < 0.05 thus the group type variable (Lot: T+BD/ T-BD) significantly influences survival time. The median survival time was 144 months for the T+BD group and 216 months for the T-BD group. The survival time (months) almost double for the T-BD group is observed according to the HR risk ratio = 2.0334 and differ significantly from the 1 value (i.e. equal risk) because the 95% CI for HR = (1.2385 to 3.3384) does not border this value.

47 patients (78.33%) of the total of 60 in the T+BD group respectively 17 patients (50.00%) of the total of 34 patients in the T-BD group reached the final event (death).

24. Electroencephalographic recording

To observe the long-term consequences of cerebral toxoplasmosis in HIV infected patients concerning brain activity, a 3-hour electroencephalography was performed, with a helmet, with 10-20 system electrodes placement on the scalp surface [16,17,18]. The participating patients were recorded for 3 hours in awake and asleep state, with 3 minutes- hyperventilation manoeuver.

The posterior background rhythm was 8Hz in the 5 patients recorded. 8Hz rhythm is at the lower limit of the alpha range and may reflect a brain dysfunction degree. It may be a direct result of HIV brain damage, opportunistic infections or cerebrovascular disease. There were no findings compatible with encephalopathy or epilepsy.

Discussions

In the this study, we aimed to highlight the clinical-evolutive particularities of 94 HIV-infected patients with cerebral toxoplasmosis, divided into 2 groups. One group consisted of HIV-infected patients diagnosed with cerebral toxoplasmosis who had other brain disorders (T+BD) and the other group consisted of long- known HIV- infected patients who developed cerebral toxoplasmosis (T-BD) without other documented brain disorders. From the data obtained, out of the group of 94 patients, 34 patients representing 36.17% suffered from cerebral toxoplasmosis due to HIV infection and 60 patients representing 63.83% suffered from multiple brain disorders in addition to cerebral toxoplasmosis. About twice as many patients suffered from several types of brain disorders.

The presence of HIV in the central nervous system contributes to the development of neurological complications, which may explain the high percentage of patients with multiple life-threatening neurological conditions. Early untreated HIV infection localizes in certain organs called "sanctuaries", where it continues to produce changes despite adequate antiretroviral treatment and serum undetectable viremia. Among such organs is the central nervous system, where due to the blood-brain barrier the penetrability of medication is low. Early implementation of cART induced a dramatic decrease in the incidence of neurological disorders.

AIDS dementia complex(ADC) was present in 37.23% of T+BD patients and when occurs particularly in children infected with HIV from birth we observe the rapid decrease of CD4 lymphocytes level. Progressive multifocal leukoencephalopathy (PML) and stroke occurred in 6 patients each representing 6.38%. TB meningitis and meningitis with Neisseria Meningitidis was identified in 4 patients, each representing 4.26% of the T+BD group. Then 2 patients each representing 2.13% had arteriovenous malformations (AVM) and polyradiculoneuritis, and only one patient had primary cerebral lymphoma (PCNSL), 1.06%.

An important aspect to mention is HIV disease stage at the diagnosis establishment. Thus in the group with multiple brain disorders (T+BD): 8.33% were diagnosed in stage A, 33.33% were staged in stage B, 58.33% in stage C. In the group with cerebral toxoplasmosis (T-BD): 5.88% were in stage A, 41.18% in stage B, and 52.94% in stage C. Since the study focuses on

cerebral toxoplasmosis, a statistically significant group was first diagnosed with cerebral toxoplasmosis and soon after tested HIV-positive and is easy to understand the increased proportion of patients in stage C, as a patient who develops cerebral toxoplasmosis is placed directly in stage C. It is observed that, more than half of the studied group is directly placed in the most advanced stage disease, having the lowest survival rates. Detecting the disease in the early stages and starting cART treatment as early as possible is extremely important for restoring the immunologic status, avoiding the virus remaining in certain organs, the so-called sanctuaries, where antiretroviral medication has a low bioavailability and, consequently, the therapeutic success is low.

Regarding the association between cerebral toxoplasmosis in HIV- infected patients with tuberculosis, out of a total of 94 patients, 50 of them had associated a form of tuberculosis (TB) representing a percentage of 53.2%. Of the TB types, as expected, the most common type of TB is pulmonary - 38.3% (36 patients), followed by extrapulmonary forms - which amounted to 15%. Among the extrapulmonary types of tuberculosis the following were observed: pleuritic TB – 4.3% (4 patients), followed by lymphatic TB - 3.2%(3 patients), digestive TB - 2.1 % (2 patients), meningitis TB - 4.3% (4 patients), miliary TB 1.1% (1 patient), and pericarditis TB 1.1% (1 patient). The risk of finding Mycobacterium tuberculosis infection did not differ significantly between the 2 groups. The clinical features of tuberculosis in the HIV-infected population are closely related to immune deficiency. As the CD4 lymphocyte level decreases, the clinical presentation changes from localized typical forms to disseminated atypical forms.

As regarding peripheral neuropathies in the studied group, 25.5% (24 patients) presented such disease. Between the two groups formed, with multiple brain disorders (T+BD) and cerebral toxoplasmosis (T-BD), in terms of associated neuropathies, the percentage values are 31.67% in the first group and 14.71% in the second group, respectively, without statistically significant differences. Neuropathies may occur in HIV, at different times in the course of the disease, depending on the stage of immunosuppression. They are the direct result of HIV infection or other viruses: cytomegalic, co-infection with virus B, C. Also, they can be the result of antiretroviral therapies, older generation, such as didanosine and stavudine, antibiotics such as dapsone and antibuberculosis drugs such as isoniazid.

The clinical features of cerebral toxoplasmosis in the studied group were focal, with focal neurological deficit in 36 patients (38.3%), generalised with fever, chills, headache, generalized tonic-clonic epileptic seizures onset in 54 patients (57.4%) ,with both types of features: generalized and focal, in 4 patients (4.3%).

In terms of clinical features, 40% of the group with multiple brain disorders (T+BD) had focal features, compared to those with cerebral toxoplasmosis (T-BD) which were 35.29% in proportion, without a statistically significant difference between the 2 groups.

Generalized features were observed in a proportion of 53.33% in the group with multiple brain disorders (T+BD) and 64.71% in the group with cerebral toxoplasmosis (T-BD). Also in the case of generalised features, there were no statistically significant differences between the 2 groups. Regarding both types of clinical features, the group with multiple brain disorders (T+BD)

are reported as 6.67 %, while in the group with cerebral toxoplasmosis (T-BD) there were no patients.

Generalized clinical features onset as generalised onset, tonic-clonic epileptic seizures were described in 12 patients, with a frequency of 12.8%. Thus 18.33 % of the group with multiple brain disorders (T+BD) presented generalised tonic-clonic epileptic seizures and 2.10% of the group with cerebral toxoplasmosis (T-BD). There is a risk of 7.408 higher to find a patient with generalized tonic-clonic epileptic seizures on the group with multiple brain disorders (T+BD) compared to the group with cerebral toxoplasmosis (T-BD). There is an association relationship between the variable generalised onset tonic-clonic epileptic seizures and the studied group.

Epileptic seizures with focal onset were described in 4 patients (4.3%) of the 94 subjects studied, a small percentage probably due to the fact that cerebral toxoplasmosis produces a noisier symptomatology with generalized epileptic seizures due to a large number of cerebral cysts spread in both hemispheres producing epileptic seizures with origin from both hemispheres resulting in generalized epileptic seizures. In comparison, focal seizures appeared at 5% in the multiple brain disorder(T+BD) group and 2,94% in the cerebral toxoplasmosis(T-BD) group, without statistically significant differences.

Motor deficits were observed with a frequency of 28.7% in 27 patients in the study group, compared to 71.3% in 67 patients who did not present motor deficits. The distribution between the 2 groups was 31.67% in those with multiple brain disorders (T+BD) and 23.53% in those with cerebral toxoplasmosis (T-BD), without a statistically significant difference between the 2 groups. The types of motor deficit encountered were: right or left hemiparesis in 20% of the group with multiple brain disorders (T+BD) and 14.71 % in the group with cerebral toxoplasmosis (T-BD), brachial monoparesis in 5% in the group with multiple brain disorders (T+BD) and in 2.94 % in the group with cerebral toxoplasmosis (T-BD). Crural monoparesis was found with a frequency of 1.67 % in the first group (T+BD) and 0% in the second (T-BD). Paraparesis and paraplegia were reported with a frequency of 3.33% in the first group (T+BD) and 2.94% in the second (T-BD) and central facial palsy (CFP) had a frequency of 1.67% in the first group (T+BD) and 2.94% in the second group (T-BD). Patients who developed motor deficit, without remission, are those patients in whom the lesions caused tissue damage in the representative functional areas and recovered with sequels.

Speech impairment are present with a frequency of 4.26% in 4 patients. Speech impairment was found with a frequency of 3.33%, at 2 patients, in the group of patients with multiple brain disorders(T+BD) 5.88% and at 2 patients, in the group with cerebral toxoplasmosis(T-BD), with no statistically significant differences between the 2 groups regarding speech impairment.

Cranial nerve palsy occurred in a minority of cases and represented 6.4%. Cranial nerve palsy in those with multiple brain disorders (T+BD) was present in 8.33% of the cases and 2.94% in those with cerebral toxoplasmosis (T-BD). Thus, nerve III injury was found in 1.67% of the group with multiple brain disorders (T+BD) and in 2.94% of the group with cerebral toxoplasmosis (T-BD), 1 patient in each group. Multiple nerves lessions III, IV, VI, IX, X was observed in 1.67%

of the cases, practically one patient in the first group (T+BD) and none in the second group (T-BD). Nerve VII injury was observed in 5% in the first group (T+BD), 3 patients, and none in the second group (T+BD). No statistically significant differences were observed between the two groups.

Of the studied group, 2.13%, 2 patients, had visual impairment: one patient had lateral homonymous hemianopia and one patient had binocular diplopia. There was no relationship between the variables: visual impairment and the group at the χ^2 test of association between two categorical variables. Their distribution between the 2 groups, is 3.33% in the group with multiple brain disorders (T+BD), meaning 2 patients, are subdivided as follows: 1.67% with lateral homonymous heminopia, represented by 1 patient, and 1.67% diplopia, represented by 1 patient. No visual impairment was reported in the toxoplasmosis cerebral (T-BD) group.

Regarding sensitivity disorders, 9.6%, 9 patients, were found to have hemihypoesthesia. A frequency of 8.33% was reported in the group with multiple brain disorders (T+BD) and 11.76% in the group with cerebral toxoplasmosis (T-BD), with statistically significant differences between the 2 groups at the χ^2 test.

Out of the group of 94 patients, gait and coordination impairment was identified with a frequency of 13.83% in 13 patients, of whom 5 patients (5.3%) presented a bicerebellar syndrome and 8 patients (8.5%) presented a right or left cerebellar syndrome. At the χ^2 test of association of two categorical variables, there was no dependent relationship between the group variable and gait and coordination impairment variable. Thus, 6.67% of the first group (T+BD) had bicerebellar syndrome and 2.94% of the second group (T-BD) developed the same syndrome. Unilateral right or left cerebellar syndrome was reported in 10% of the T+BD group and in 5.88% of the T-BD group. There were no statistically significant differences in gait and coordination impairment between the multiple brain disorder (T+BD) and cerebral toxoplasmosis (T-BD) groups.

Clinical manifestations such as involuntary movements were recorded in 2 patients out of 94, with a frequency of 2.1%. We observed hemibalism with a frequency of 1.67%, 1 patient, and chorea 1.67%, 1 patient. Involuntary movements were observed on clinical examination with a frequency of 3.33% in the group with multiple brain disorders (T+BD) and 0% in the cerebral toxoplasmosis group(T-BD).

Applying the Wilcoxon Signed Rank test, regarding the viremia (expressed in log), it was observed the existence of differences between the median level values of both groups: with multiple brain disorders (T+BD) and only with cerebral toxoplasmosis (T-BD) in the sense that the median level values before treatment were higher for both groups than the viremia level values at the end of combined treatment(antitoxoplasma and antiretroviral). These results can be explained by the administration of antiretroviral therapy at the same time as the antitoxoplasma treatment. The regimen of therapy, correctly administered, suppressed the viral load of HIV copies and decreased the viremia and consequently, led to an immunological status improvement for most patients.

The Wilcoxon Signed Rank test was used to highlight the differences in CD4 values level of the two groups (samples) at establishing the diagnosis of cerebral toxoplasmosis and at the end

of the combined treatment of cerebral toxoplasmosis and antiretroviral therapy. Thus, for both groups, CD4 lymphocytes level at the end of treatment are higher than at diagnosis establishment.

From the study group of 94 patients, 71.3% of the patients underwent imaging investigations, computer tomography (CT) and magnetic resonance imaging (MRI). Cerebral imaging was performed in 75% of the patients, at 45 patients out of the group of 60 patients with multiple brain disorders (T+BD) and in the group with cerebral toxoplasmosis (T-BD), imaging was performed in 64.71%, representing 22 patients out of the group of 34. Out of the 71.3% (67 patients), 35 of them repeated the brain imaging initially performed for follow-up. Brain imaging for follow-up was performed in 36.67% of patients from the group with multiple brain disorders (T+BD), 22 patients and 38.24%, in 13 patients from the group with cerebral toxoplasmosis (T-BD), without statistically significant difference between the 2 groups.

In the studied group, 4.3%, 4 patients underwent brain biopsy due to atypical imaging findings not consistent with cerebral toxoplasmosis lesions and cerebral toxoplasmosis diagnosis was confirmed in all 4 cases. Brain biopsy was performed in 1.67% of the patients in the group with multiple brain disorders (T+BD), representing 1 patient, and in the group with cerebral toxoplasmosis (T-BD) in 8.82% of the patients, representing 3 patients. There were no statistically significant differences between the groups.

According to the obtained data regarding treatment regimen administered, the majority received treatment with trimethroprim-sulfamethoxazole 56.4%, pyrimethamine 25.5%, azithromycin 14.9%, clindamycin 3.2%. The treatment regimen received by the majority of patients, 81.9%, is the same at the current guideline indications, in which the first line of treatment is trimethroprim-sulfamethoxazole or pyrimethamine associated with sulfadiazine, and the second line includes azithromycin or clindamycin. Sometimes, therapy administration represents the therapeutic evidence for indirect confirmation of cerebral toxoplasmosis diagnosis, with monitoring the response to treatment under clinical and imaging aspect, at 14-days distance.

Regarding adherence to antiretroviral therapy, 51 patients (54.3%) were compliant to antiretroviral therapy. Distribution between the 2 subgroups: 43.33% of patients in the group with multiple brain disorders (T+BD) were compliant and adheredent to the antiretroviral medication regimen and 73.53% in the group of patients with cerebral toxoplasmosis (T-BD) were compliant to the treatment. The compliance in the group with multiple brain disorders (T+BD) is 3.636 times lower than in the group with cerebral toxoplasmosis (T-BD).

The outcome under treatment was favourable in 54.3% of the cases, representing 51 patients, while in 45.7% of the cases, representing 43 patients, the evolution was unfavourable, with worsening of the symptoms. More than half of the patients had a favourable outcome. Regarding the favourable outcome, it is inclined towards the group with cerebral toxoplasmosis (T-BD) in 73.53% of cases compared to 26.47% of patients in the group with multiple brain disorders (T+BD), and it is statistically significant.

Following cerebral toxoplasmosis 64 patients, representing 68.1%, died while 30 patients remained alive, representing 31.9%. Survival after cerebral toxoplasmosis, applying χ^2 test for association between two categorical variables shows that the proportion of patients who died with

multiple brain disorders (T+BD) group, representing 78.33% differed significantly from the proportion of patients who died in the cerebral toxoplasmosis (T-BD) group, 50%, with a 3.615-fold higher risk of patients in the T+BD group compared to the T-BD group.

From the Kaplan-Meier curve plot, the median survival time survival was 144 months for the multiple brain disorders (T+BD) group, and almost double, 216 months, for those who suffered only from cerebral toxoplasmosis (T-BD). Out of a total of 60 patients in the T+BD group, 47 patients (78.33%) and 17 patients (50.00%) out of a total of 34 patients in the T-BD group reached the final event of death. The two survival curves differ significantly: Chi-square = 6.8592, df= l, p = 0.0088 < 0.05, i.e. and the group membership (T+BD/ T-BD) significantly influences survival time.

Conclusions

1. Nervous system injury in HIV infection are varied, complex and are due to a number of viruses, bacteria, parasites or fungi. The most important disorders are: AIDS encephalopathy (AIDS dementia complex), primary cerebral lymphoma, progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, meningitis (TB, Cryptococcus neoformans, Neisseria meningitidis), stoke, arteriovenous malformations, polyradiculoneuritis.

2. Cerebral toxoplasmosis is the most common opportunistic parasitic infection of the central nervous system in HIV-infected patients with severe immunodepression (CD4 lymphocytes levels below 100 cells/mm^3). Clinical picture may take the form of subacute or chronic meningitis, diffuse encephalitis with or without epileptic seizures, space-occupying processes (abscesses), stoke and myelopathy. The prevalence of toxoplasmosic encephalitis can reach 40% in the absence of ARV treatment.

3. The study included a group of 94 patients, divided into two groups: one (T+BD) with 60 patients with cerebral toxoplasmosis associated with other brain disorders, and the other (T-BD) including 34 patients with cerebral toxoplasmosis. The two groups were comparatively analysed regarding the onset of neurological symptoms, diagnosis, clinical outcome after treatment and cure/survival rate.

4. The stage of HIV infection at the diagnosis establishment explains that neurological impairment is directly related to immunodepression degree, thus in the T+BD group: 8.33% were diagnosed in stage A, 33.33% were staged in stage B and 58.33% in stage C, and in the T-BD group with cerebral toxoplasmosis: 5.88% were in stage A, 41.18% in stage B, 52.94% in stage C, so that in both groups, stage C (AIDS disease) prevail.

5. Of the T+BD group, the most common disease associated was AIDS encephalopathy (AIDS complex dementia) in 35 patients (37.2%), followed by progressive multifocal leukoencephalopathy and stroke in 6 cases each (6.38%), 4 cases each (4.26%) of meningitis (Neisseria Meningitidis and TB), 2 cases each (2,13%) of arteriovenous malformation (AVM) and polyradiculoneuritis, described as a complication of HIV infection, and one case (1,26%) of primary cerebral lymphoma.

6. The proportion of patients with generalized tonic-clonic epileptic seizures at onset was 18.33% in the T+BD group and is statistically significantly different from the proportion of patients, 2.10%, in the T-BD group with cerebral toxoplasmosis. Regarding epileptic seizures with focal motor or non-motor onset, there were no statistically significant differences between the two subgroups.

7. Motor deficit was observed in almost one third of the study group patients, being the most frequent reason for presentation to the hospital. The types of motor deficit encountered were: right or left hemiparesis in 20% of the T+BD group and 14.71% in the T-BD group, brachial monoparesis (5% /2.94%), crural monoparesis (1.67%,/0), paraparesis and paraplegia were reported with a frequency of 3.33% in the first group and 2.94% in the second, and central facial palsy had a frequency of 1.67% in the first group and 2.94% in the second.

8. Other clinical features of onset of cerebral toxoplasmosis were: speech impairment in 4.26% of cases, cranial nerve palsy in 6.4% of cases, visual impairment was present in 2.13% of cases, about 10% of patients were recorded with sensitivity impairment, gait and coordination impairment were found in 13.83% of cases, and involuntary movements in 2.1% of cases.

9. Other toxoplasmosis localisations, simultaneous with cerebral involvement, were ocular 3.33% in T+BD group and 2.94% in T-BD group, and lymphatic l .67% in T+BD group.

10. About 60% of patients in the group presented comorbidities: 66.67% in the T+BD group and 47.06% in the T-BD group, with a simultaneous evolution independent of the cerebral disorders, but with a key role in worsening the clinical status with poor outcome for most patients. Tuberculosis, the most frequent severe opportunistic bacterial infection, was an important aggravating factor with an important influence on the survival rate of these patients.

11. The data obtained are unfavourable for the T+BD group, due to the multiple brain disorders and due to increased frequency of comorbidities. Therapeutic efforts have been focused on cerebral toxoplasmosis treatment, the only curable disease among those mentioned before. Thus, patient deaths occurred in a proportion of 68.1%, with statistically significant differences between the 2 groups: 78.33% of patients died in the group with multiple cerebral disorders T+BD and 50% in the group with cerebral toxoplasmosis T-BD.

12. Early begining of antiretroviral therapy suppressed HIV multiplication leading to an increase in CD4 cell level count with a significant improvement of patients immune status, improving the outcome according to the Wilcoxon Signed Rank test. Patients adherence to ARV treatment played a key role in patients long-term prognosis and outcome.

13. Average survival time was 144 months in multiple brain disorders(T+BD) group and 216 months in cerebral toxoplasmosis group(T- BD). The risk of death in the multiple brain disorders group is twice higher than in the cerebral toxoplasmosis group. Apropriate cerebral toxoplasmosis therapy, with serological and imaging surveillance, has an increased rate of healing and long-term survival without sequelae. This conclusion is supported by the results of the Kaplan-Meier curve.

14. Three-hour electroencephalographic recordings were performed for the first time in this type of patients. Five of the 30 surviving patients agreed to participate in the

electroencephalographic recordings during recovery or after healing. The EEG recorded did not reveal any pathological findings, like encephalopathy or epilepsy. Establishing the right treatment (antitoxoplasma and antiretroviral), has induced disease remission, achievement of an appropriate immunologic status, with good long-term outcome.

15. The restoration of cell-mediated immunity through the introduction of ARV treatment (cART) has reduced the risk of toxoplasmosis, allowing prophylaxia interruption. The occurrence risk of inflammatory reconstitution immune syndrome, presenting a paradoxical worsening of toxoplasmosis symptoms or other previously diagnosed brain disorders, requires interdisciplinary collaboration (infectious disease- neurology) in these patients cases.

16. Modern ARV treatment, easy to administer, has significantly reduced the rate of immunodepression, with an important decreasing rate of opportunistic infections. In this context, brain disorders are also becoming increasingly rare, so the results of current research may represent a diagnostic and therapy guide for possible new cases of advanced HIV infection with severe immunodepression (C-AIDS).

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Appendix- Publications list

Personal published articles from the PhD thesis topics ISI and BDI

1. Raluca-Ileana Rosioru (Istrate), Veronica-Violeta Rosioru, Lucian Cristian Petcu, Sorin Rugina, Considerations Over Cerebral Toxoplasmosis and Other Cerebral Disorders in HIV Infected Patients, Volume 30 (2024): Issue 1 (february 2024), pg. 5 – 11, doi: 10.2478/arsm-2024-0002
2. Raluca-Ileana Rosioru(Istrate), Lucian Cristian Petcu, Aurelia Hangan, Sorin Rugina, Epileptic Seizures in People with HIV- Related Toxoplasmosis and Other Cerebral Disorders, Volume 30 (2024): Issue 1 (february 2024), pag. 19 – 23, doi: 10.2478/arsm-2024-0004