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Prognosis of fungal infection of central nervous system in HIV-infected patients: a retrospective study of 77 patients in Ukraine

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Abstract

Introduction: We aimed to describe the epidemiological, clinical, laboratory characteristics, and outcomes of central nervous system (CNS) mycosis in patients with human immunodeficiency virus (HIV) and to determine characteristics associated with a higher risk of death. Retrospective data from 77 case histories of HIV-infected patients with neurological symptoms caused by various fungi including *Candida* and *Cryptococcus* in Dnipro, Ukraine, were analysed as a case-control study with 40 deceased individuals considered as cases and 37 patients with favourable outcome (survivors) considered as controls.

Material and methods: Fungi in cerebrospinal fluid (CSF) were detected with traditional culture methods. Multivariate analysis used (1) binary logistic regression with survivor/dead as a dependent variable and (2) a classification and regression tree (CRT method).

Results: A combination of fungal infection with other infections of CNS (dual and triple coinfection) was diagnosed in most cases (n = 53, 68.8%), while the proportion of co-infection was somewhat lower among survivors (59.5%). Clinical manifestations were non-specific. Risk of death was higher among those with tuberculosis (AOR = 2.7, 95% CI: 1.0-7.5) and lower among those infected with Epstein-Barr virus (EBV) (AOR = 0.3, 95% CI: 0.1-1.0) and among patients on ART (AOR = 0.2, 95% CI: 0.1-0.8). Risk of death significantly decreased over time. The classification tree shows that among HIV-mycosis neurological patients not on ART with tuberculosis, the risk of death constituted 75%, while among patients on ART with EBV-infection, all patients survived.

Conclusions: Opportunistic mycoses remain an important clinical challenge among immuno-compromised patients especially those who were diagnosed with HIV late, failed to get antiretroviral therapy, and developed tuberculosis.

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Key words: opportunistic mycoses, central nervous system diseases, fatal outcome, coinfection, candidiasis, HIV, antiretroviral therapy, opportunistic infections.

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Introduction

Opportunistic infections are among the major problems faced by human immunodeficiency virus (HIV)-infected patients and a major cause of death [1], especially in countries with high HIV incidence and reduced access to antiretroviral therapy [2].

Opportunistic infections of the central nervous system (CNS) are common complications of advanced immunodeficiency [3, 4] in individuals with human immunodeficiency virus type 1 (HIV-1) infection. Neurological manifestations are seen in 10% to 20% of symptomatic HIV-1 infection, while prompt diagnosis and treatment of these disorders are critical [5]. Additionally, in the era of highly active antiretroviral therapy (HAART), neurological manifestations of HIV have changed in presentation and epidemiology [6], and the aetiological composition of HIV-associated neurological diseases varies by region of the world [1, 7-9].

Fungal infections including *Cryptococcus*, *Candida*, *Histoplasma*, and *Aspergillus* remain a challenge among other opportunistic infections [10] due to the high rate of related morbidity and mortality [11, 12]. Studies based on autopsies of immunocompromised patients show that fungal infection can be found in 9% of autopsy cases with the brain being the most common single organ affected by fungi [13]. Species of *Candida* and *Aspergillus* remain the most common agents of invasive fungal infections [14]. The increased spread of candidal infection might be due to the emergence of resistant species and the acquisition of resistance in previously susceptible species [15]. The CNS mycosis may be disseminated (cryptococcosis, coccidioidomycosis, etc.), focal (aspergillosis, zygomycosis, etc.), or multifocal (candidiasis) [11].

Fungal encephalitis lesions were characterised by deep damage and poor regeneration of neurons, which can be the cause of severe clinical manifestations and high mortality [16]. Clinical manifestations of fungal infection of the CNS have great variability which include abscesses, meningitis or meningoencephalitis, focal masses, ischaemic (commonly) or haemorrhagic (uncommonly) stroke/vasculitis, immune reconstitution inflammatory syndrome (IRIS), progressive myelopathic syndromes, and arachnoiditis [17].

Along with studies pointing to the high risk of death among patients with brain damage caused by various fungi [10], little is known about other predictors of survival among these patients. Clinical and laboratory characteristics and their discrepancies between survivors and fatal cases have also not been thoroughly studied.

We review socio-demographic, clinical, and laboratory characteristics of HIV patients with fungal infection of CNS with the aim to identify those able to predict the outcome. The study is conducted in Ukraine, a country with an HIV epidemic characterised by high incidence and prevalence [18]. This epidemic was initially propelled by injection drug use, but heterosexual transmission has become a major driver of new infections [19].

Material and methods

This analysis was based on the retrospective data from 77 cases of HIV-infected patients with neurological symptoms caused by fungi revealed in cerebrospinal fluid (CSF) culture between 2010 and 2016 in Dnipro city and Dnipropetrovsk regional clinical centres for HIV/AIDS prevention and control. Among these, 40 cases were with fatal outcome (deceased individuals) and 37 cases with favourable outcome (survivors).

All cases of fungal infection in CSF were diagnosed with traditional culture methods. For the isolation of colonies, the cerebrospinal fluid was centrifuged and 0.1 ml of it was inoculated on Sabouraud dextrose agar. The plates were incubated at 37°C for 2-3 days. Several colonies suspected as *Candida* were inoculated to a liquid medium to identify filamentous growth specific for *Candida*. To determine the number of yeast cells in 1 ml the counted number of colonies on the plate was multiplied by 10. Microscopy of Gram-stained thin smears of the matter from isolated colonies was aimed at detection of budding yeast-like cells and pseudohyphae showing regular points of constriction. Gram-stained thin smear preparations of cerebrospinal fluid before microscopy were dried and fixed with methyl alcohol. Identification of *Candida* species was based on the biochemical properties of the fungi. Identification of other concomitant CNS infectious agents, in addition to fungi, in CSF and/or autopsy material was carried out using polymerase chain reaction and culture methods.

The analysis is limited to those characteristics which were routinely collected and registered in medical records. These included patient demographics and clinical characteristics, comorbidities, medications, and HIV-specific information such as CD4 and viral load (where available). No additional measurements were taken for the study. The Bioethics Commission of Dnipropetrovsk Medical Academy (Ukraine) reviewed and approved the study.

Descriptive statistics of categorical and metric variables were used to compare two groups of patients. In bivariate analysis, variables associated with disease outcome were revealed. Multivariate analysis used binary logistic regression with survivor/dead as a dependent variable and classification tree with CRT method. All statistical analyses were performed using SPSS version 21.

Results

All 77 patients with fungal and potentially *Candida* infection of CNS were adults with mean age 38.3 years (ranging from 19 to 59 years; standard deviation [SD] = 7.5). Most of the patients were aged 35-44 years. Males constituted the majority (n = 48, 62.3%), with 67.5% being males among those who died.

Candida was biochemically confirmed for 37 patients; other fungal agents were considered as various yeasts. A combination of fungal infection with other infections of CNS (dual and triple coinfection) was diagnosed in most

cases (n = 53, 68.8%) while the proportion of co-infection was somewhat lower among survivors (59.5%) than among the deceased patients (77.5%) (Table 1).

Cerebral tuberculosis was identified in 31 patients (58.5% of those with coinfection), 21 (67.7%) of them died in hospital. Epstein-Barr virus (EBV) DNA was detected in the CSF of 15 (28.3%) individuals; progressive multifocal leukoencephalopathy (PML) caused by John Cunningham virus (JCV) was diagnosed in 6 (11.3%) patients, *Toxoplasma* and *Cryptococcus* were accountable for four (7.5%) cases each, and herpes simplex virus (HSV) and bacterial meningitis were present in three (5.7%) cases each. Two patients (3.8%) with fungal infection were also diagnosed with a stroke.

The most common clinical manifestations in patients with fungal monoinfection were a headache (23 of 24 patients – 95.8%), coordination disorders: vertigo, gait unsteadiness, and coordination test failures (19 persons – 79.3%); positive meningeal symptoms (mainly neck stiffness) were observed in 10 (41.7%) patients; impaired consciousness occurred in three (12.5%) cases; cognitive disorders in 4 (16.7%) cases; visual disturbances were detected in six (25.0%) patients; deficiency of cranial nerves in eight (33.3%); convulsions in three (12.5%); dysarthria in three (12.5%), tremor of the tongue in one patient (4.2%); and eyelid tremor in one patient as well (4.2%).

Among those for whom the route of HIV transmission was known, 66.7% were people who injected drugs; this percentage was higher (74.2%) among the survivors. For half of the deceased patients, the route of transmission was unknown because their HIV-infection was diagnosed just before the death and their physical state did not allow undertaking a detailed interview.

The time span between the detection of HIV and the development of CNS fungal infection averaged 3.7 (SD = 4.5) years ranging from 0 to 17 years with median time constituting one year and no significant difference found between the groups of those who died and who survived (Table 1). In almost half of the patients who died (45.0%) and more than a third of the surviving patients (35.1%), HIV-infection was diagnosed late, within the same year or simultaneously with the identification of CNS manifestations. Therefore, only some patients had HIV viral load measurements, and ART coverage before the appearance of neurological symptoms was rather low (n = 20, 26.0%): 15.0% of those who died and 37.8% of survivors.

HIV viral load measurements were available for 23 patients (29.9%) (Table 1). Most of these patients (n = 20, 98.2%) had HIV viral loads above 50 copies/ml. All deceased patients had viral load counts ≥ 50 copies/ml. Median HIV viral load was 135,537 copies/ml (range 40-1,926,802). The median viral load was higher in deceased patients (185,971 copies/ml; range 5309-478,504) than in survivors.

Most patients (n = 48, 62.3%) had an absolute CD4 count < 50 cells/μl, which corresponded to severe immunosuppression. Only a few patients (n = 5, 6.5%) had an absolute CD4 count above 200 cells/μl. Median CD4 cell count was 50 cells/μl (range 1-461) in the whole group and among the surviving patients, and 34 cells/μl (range 1-216) among the patients who died.

Comparison of immunologic and viral load indicators between the groups of patients with fungal monoinfection and patients with coinfection (Table 2) demonstrated no significant difference between the groups ($p > 0.05$).

Almost half of the patients (n = 38, 49.4%) had pleocytosis: increased CSF white blood cells (WBCs) were found in 50.0% of deceased patients and 48.6% of survivor-patients (Table 1). Median CSF WBCs was 14.0 per mm^3 (range 0-853). Deceased patients had higher median CSF WBCs – 21.0 per mm^3 (range 0-853). Parameters of the cerebrospinal fluid in patients with *Candida* monoinfection (Table 1) did not show differences between those who died and those who survived ($p > 0.05$). Increased CSF WBCs were found in about one-third of patients with monoinfection: in 33.3% of patients who died and in 26.7% of survivors. In the case of coinfection, these proportions were 54.8% and 63.6%, respectively. However, comparison of CSF WBCs between all patients and patients with fungal monoinfection shows that pleocytosis counts were much higher among those with coinfection than among patients with fungal monoinfection.

In the group of patients who survived, the maximum number of WBCs in the CSF was 148.0 per mm^3 in patients with monoinfection and 496.0 per mm^3 in patients with coinfection, and mean CSF WBC, respectively, was 26.3 (SD – 44.4) cells/mm^3 and 45.5 (SD – 105.6) cells/mm^3. Among the fatal cases, these rates were correspondingly: 92.0 cells/mm^3 and mean CSF WBCs – 17.4 (SD – 29.5)/mm^3 in patients with monoinfection and 853.0 cells/mm^3 and mean CSF WBCs – 101.2 (SD – 177.0) cells/mm^3 in the case of coinfection.

Mean CSF protein concentration was 0.3 (SD – 0.2) g/l and was not different in survivors and deceased patients. The CSF glucose level ranged between 1.2 and 4.8 mmol/l and was normal in most patients and did not differ much between those who died and those who survived (2.4 [SD = 0.8] mmol/l vs. 2.7 [SD = 1.2] mmol/l).

Multivariate analysis using binary logistic regression model with alive/dead dependent variable (see Table 3) revealed that the risk of death was higher among those with tuberculosis (AOR = 2.7, 95% CI: 1.0-7.5) and lower among those infected with Epstein-Barr virus (AOR = 0.3, 95% CI: 0.1-1.0) and patients on ART (AOR = 0.2, 95% CI: 0.1-0.8).

Risk of death significantly decreased over time; however, because this association did not confound those described above, and the year of neurological diagnosis was not entered in the final regression model.

A classification tree built using the CRT method (see Figure 1) allowed for 71.4% accuracy of prediction and provided estimated risks for all the combinations of ART, tuberculosis, and EBV. As the decision tree shows, among HIV-mycosis neurological patients not on ART with tuberculosis, the risk of death constituted 75%, while only 12.5% of patients not on ART with EBV-infection died. Among HIV-mycosis neurological patients on ART, if tuberculosis was also diagnosed, the risk of death was 50% while among patients on ART with EBV-infection, all patients survived.

Table 1. Characteristics of 77 patients with HIV and fungal infection of central nervous system in Dnipropetrovsk region, Ukraine, 2010-2016

Characteristic	Total	Deceased	Survivors
Patients, *n* (%)	77 (100)	40 (51.9)	37 (48.1)
Age, mean (SD), years	38.3 (7.5)	37.7 (7.6)	39.0 (7.5)
Age, range, years	19-59	25-59	19-56
Male gender, *n* (%)	48 (62.3)	27 (67.5)	21 (56.8)
HIV transmission, *n* (% among those with known mechanism)			
Parenteral (PWID)	34 (66.7)	11 (55.0)	23 (74.2)
Sexual	17 (33.3)	9 (45.0)	8 (25.8)
Total, *n*	51 (100)	20 (100)	31 (100)
Unknown transmission mechanism, *n* (%)	26 (33.7)	20 (50.0)	6 (16.2)
Duration of the period from the diagnostics of HIV-infection to the development of neurological symptoms, number of patients, *n* (%)			
> 9 years	9 (11.7)	6 (15.0)	3 (8.1)
5-9 years	19 (24.7)	7 (17.5)	12 (32.4)
1-4 years	17 (22.1)	9 (22.5)	9 (24.3)
< 1 year	32 (41.5)	18 (45.0)	13 (35.1)
Mean duration (SD), years	3.7 (4.5)	3.4 (4.6)	4.0 (3.5)
Median duration (range), years	1.0 (0-17)	1.0 (0-17)	3.5 (0-17)
Immunologic status: CD4 cell count, *n* (%), cells/μl interval (1)			
< 200	72 (93.5)	39 (97.5)	33 (89.2)
≥ 200	5 (6.5)	1 (2.5)	4 (10.8)
CD4 cell count, *n* (%), cells/μl interval (2)			
0-50	48 (62.3)	27 (67.5)	21 (56.8)
51-100	11 (14.3)	6 (15.0)	5 (13.5)
101-200	13 (16.9)	6 (15.0)	7 (18.9)
201-500	5 (6.5)	1 (2.5)	4 (10.8)
Mean CD4 cells/μl (SD)	72.9 (94.0)	51.3 (52.4)	96.2 (120.9)
Median CD4 cells/μl (range)	50 (1-461)	34 (1-216)	50 (4-461)
HIV viral load, interval, *n* (%) copies/ml			
< 50	3 (13.0)	0 (0.0)	3 (8.1)
≥ 50	20 (87.0)	11 (100)	9 (91.9)
Total, *n* (%)	23 (29.9)	11	12
Mean HIV viral load copies/ml (SD)	255,032 (438,584)	192,796 (141,842)	312,082 (599,164)
Median HIV viral load copies/ml (range)	135,537 (40-1,926,802)	185,971 (5,309-478,504)	70,362 (40-1,926,802
Median HIV viral load copies/ml (range) log10	5.1 (1.6-6.0)	5.3 (3.7-5.7)	4.8 (1.6-6.1)
Receiving ART, *n* (%)	20 (26.0)	6 (15.0)	14 (37.8)
Fungal monoinfection, *n* (%)	24 (31.2)	9 (22.5)	15 (40.5)
Coinfection with other pathogens, *n* (%)	53 (68.8)	31 (77.5)	22 (59.5)
Structure of coinfection with other pathogens in central nervous system			
MBT	31 (58.5)	21 (67.7)	10 (45.5)
EBV	15 (28.3)	4 (12.9)	11 (50.0)
Bacterial infection (purulent meningitis)	3 (5.7)	3 (9.6)	0 (0.0)
Toxoplasma	4 (7.5)	1 (3.2)	3 (13.6)
Cryptococcus	4 (7.5)	3 (9.6)	1 (4.5)
CMV	1 (1.9)	1 (3.2)	0 (0.0)
JCV (PML)	6 (11.3)	6 (19.4)	0 (0.0)
HSV	3 (5.7)	3 (9.6)	0 (0.0)

Table 1. Cont.

Characteristic	Total	Deceased	Survivors
Characteristic of CSF			
Presence of pleocytosis (increase of CSF WBCs), *n* (%)			
Among all	38/77 (49.4)	20/40 (50.0)	18/37 (48.6)
Among patients with fungal monoinfection	7/24 (29.2)	3/9 (33.3)	4/15 (26.7)
Among patients with fungal coinfection	31/53 (58.5)	17/31 (54.8)	14/22 (63.6)
Mean CSF WBCs/mm^3 (SD)			
Among all	67.6 (136.5)	89.1 (164.5)	42.7 (90.9)
Among patients with fungal monoinfection	22.7 (38.4)	17.4 (29.5)	26.3 (44.4)
Among patients with fungal coinfection	78.5 (152.7)	101.2 (177.0)	45.5 (105.6)
Median CSF WBCs/mm^3 (range)			
Among all	14.0 (0-853.0)	21.0 (0-853.0)	10.5 (0-96.0)
Among patients with fungal monoinfection	3.5 (0.0-148.0)	5.0 (1.0-92.0)	3.0 (0.0-148.0)
Among patients with fungal coinfection	14.0 (0-853.0)	21.0 (0-853.0)	14.0 (0.0-496.0)

PWID – people who inject drugs, MBT – Mycobacterium tuberculosis, EBV – Epstein-Barr virus, CMV –, JCV – John Cunningham virus, PML – progressive multifocal leukoencephalopathy, HSV – herpes simplex virus, CSF – cerebrospinal fluid culture, WBCs – white blood cells

Table 2. Immunologic and viral load status of patients with fungal mono-infection and patients with fungal coinfection

Characteristic	Monoinfection	Coinfection
CD4 cell count, *n*	24	53
CD4 cell count interval, *n* (%), cells/μl		
0-50	16 (66.6)	33 (62.3)
51-100	4 (16.7)	7 (13.2)
101-200	4 (16.7)	8 (15.1)
201-500	0 (0.0)	5 (9.4)
Mean cells/μl (SD)	54.0 (51.1)	81.4 (107.4)
Median cells/μl (range)	42.0 (4.0-178.0)	50.0 (1.0-461.0)
HIV viral load counts, *n*	7	16
HIV viral load, interval, *n* (%) copies/ml		
< 50	0 (0.0)	2 (12.5)
≥ 50	7 (100.0)	14 (81.3)
Mean HIV viral load copies/ml (SD)	365,822 (698,629)	206,562 (280,465)
Median HIV viral load copies/ml (range)	74,509 (11,458-1,926,802)	155,384 (40-1,146, 096)

Table 3. Binary logistic regression of the risk of death among HIV patients with neurological complications caused by yeasts

Independent variable	Values	Number of patients	Deaths		AOR (95%CI)	*p*-value
			n	%		
ART	No	56	34	61	1.0 (ref)	0.016
	Yes	21	6	29	0.2 (0.1-0.8)	
TB	No	46	19	41	1.0 (ref)	0.060
	Yes	31	21	68	2.7 (1.0-7.5)	
EBV	No	62	36	58	1.0 (ref)	0.046
	Yes	15	4	27	0.3 (0.1-1.0)	

ART – antiretroviral therapy, TB – tuberculosis, EBV – Epstein-Barr virus

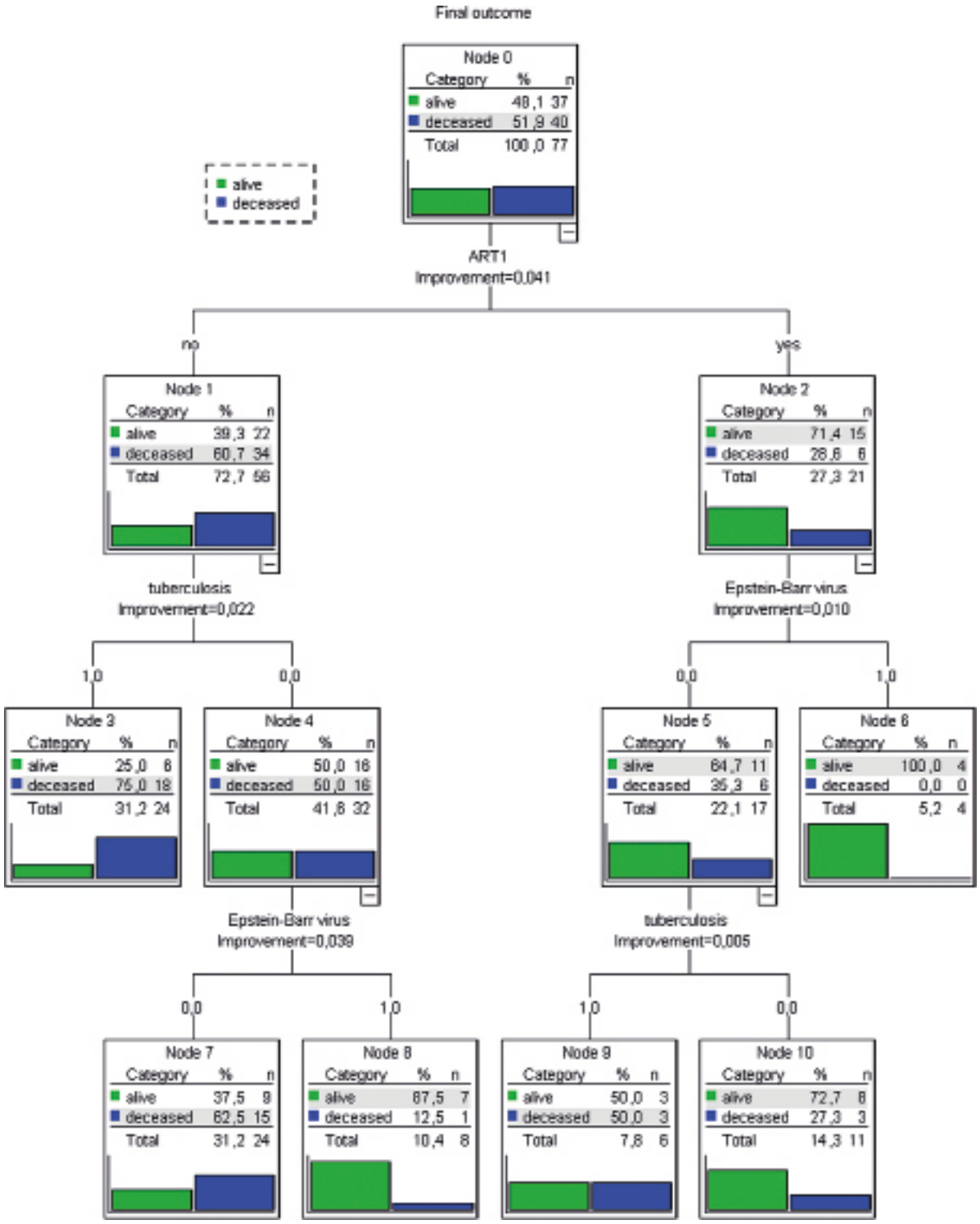

Figure 1. Classification tree of final outcomes of neurologic complications caused by fungal infections among HIV patients, CRT method, Dnipropetrovsk HIV hospital

Discussion

The conducted analysis of 77 HIV patients with neurological complications caused by various fungi revealed that all the cases developed in patients with expressed immunosuppression, which is consistent with other studies [10]. The emergence of invasive fungal infections might be precipitated by various factors. Late diagnostics and no prophylaxis to prevent invasive candidiasis [20] along with absence of ARV treatment was quite widespread among the considered patients. Many patients with HIV in Ukraine were infected due to use of home-made opiate drugs [19] injected with used syringes and needles. An additional risk factor emphasised in the literature [20] may be related to the use of central venous catheters while providing intensive care. If those catheters are not removed in a timely manner, the risk of invasive infections might increase.

In most cases, invasive fungal infections of CNS were diagnosed in combination with other infections, which complicated an objective assessment of clinical and laboratory characteristics. Additionally, laboratorial distinguishing between various fungi remains challenging [21-23].

The considered cases of fungal infections of the central nervous system were marked with high case fatality (52%). The risk of death was higher among patients with tuberculosis coinfection whereas getting antiretroviral therapy and being infected with Epstein-Barr virus were associated with lower case fatality. Findings related to ART and tuberculosis are consistent with published research because antiretroviral therapy has a known beneficial effect on the outcomes of HIV-associated neurological complications [24, 25]. Tuberculosis remains a risk factor of death among HIV patients, especially in poorer countries [26-28].

Epstein-Barr virus was mentioned among other coinfections found in cerebrospinal fluid in association with increased mortality [29]. While this contradicts our findings, no interaction of EBV and yeasts was assessed in the mentioned study, and although both agents are mentioned in several studies devoted to HIV-related clinical manifestations, none of them considers the combined impact of EBV and fungi. We hypothesise that the activation of cellular immunity as a component of EBV infection might impact the response to agents of opportunistic infections. T-cells bear functional defects [30], and natural killers decrease in all stages of HIV infection [31] while the Epstein-Barr virus infection is characterised by elevated cytotoxic/suppressor (CD8) T cells, natural killer (CD16) cells, and helper (CD4) T cells [32, 33], which are found both at the onset of the infection and over time [34]. The T-cell populations activated in EBV can be effective in attacking various fungi: CD8+ mediates the antifungal activity against *Candida albicans* [35]; with regard to *Cryptococcus neoformans*, the fungistatic role of CD4+, CD8+, and CD16/56+ lymphocytes was shown *in vitro* and *in vivo* [36, 37], and CD8+ T cells were shown to independently mediate an inflammatory response [38].

Clinical manifestations were found to be non-specific and comprising fever, headache, neck stiffness, and mental status impairment similarly to those reported by other authors [14] along with others which include vomiting, visual alterations, paralysis of cranial nerves, and confusion [39]. This makes clinical diagnosis challenging, especially because fungal infections generally have a subacute onset [40] and present similarly to various bacterial infections [41]. In HIV patients, headache and fever can be unique symptoms, and only CD4 count can help with diagnosis [42].

Our finding that patients with fungal infections had pleocytosis counts much higher in cases of coinfection suggests that the cause of pleocytosis may be due to other factors, first of all, mycobacterial infections and causative agents of purulent meningitis. However, pleocytosis and hypoglycorrhachia in fungal meningitis might be indistinguishable from that seen in tuberculous meningitis [43].

While most of the patients were middle-aged men with the majority having experience of injection drug use, these characteristics are not associated with the risk of neurological complications or increased risk of death, they are just the attributes of the current group of HIV-patients in Ukraine.

The study has several limitations. The most important of them is related to small number of study participants, which makes establishing associations more difficult. Additionally, because of late HIV diagnosis some of the risk factor data and other measurements were missing for a substantial part of the group. Due to challenging laboratory diagnostics we were not always sure regarding a particular species causing the fungal infection, so we have to relate our findings to yeast fungal infections in general.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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