Comparative Analysis of Clinical and Laboratory Parameters and Assessment of Antiretroviral Therapy Effectiveness in HIV-Associated Cryptococcal Meningoencephalitis in the Case of Immune Inflammation Syndrome

D.A. Mustafaeva[1], L.N. Tuychiev[2], E.I. Musabaev[3], T.S. Zaytseva[1], K.S. Mukhamedov[4]

[1]MD, PhD, Senior researcher, Republican AIDS Center, Tashkent, Uzbekistan, [2]MD, Professor, Department of Infectious diseases, Rector of Tashkent Medical Academy, Tashkent, Uzbekistan, [3]MD, Professor, Virology Research Institute, Tashkent, Uzbekistan, [4]MD, PhD, Associate professor, Department of Phthisiology, Tashkent medical Academy, 2 Farobiy Str., Tashkent, Uzbekistan

Abstract

Cryptococcal meningoencephalitis is an opportunistic mycosis. Earlier in medical practice single cases of the disease were encountered, now the problem becomes more and more urgent due to the increase in the HIV infection spread, as persons with impaired immune systems are affected. In most cases, cryptococcosis refers to HIV-associated diseases. However, today there are unexplored clinical, virologic immunological aspects of HIV-associated cryptococcosis. The comparative rarity of the multi-organ nature of the lesion, the lack of objective clinical and laboratory data that allow to timely suspect and confirm a cryptococcal infection, lead to errors in the diagnosis and treatment of this pathology. The main goal of our work is to study the prevalence of HIV-associated cryptococcosis, the clinical and laboratory features of HIV-associated cryptococcosis in patients associated with inflammatory immune restoration syndrome to increase the diagnosis and treatment efficiency in Uzbekistan.

Keywords: *HIV infection, cryptococcal meningoencephalitis, immune inflammation syndrome, antiretroviral therapy.*

Introduction

The development of deep mycoses in HIV-infected people is one of the most pending problems of the last decade. The combination of these two infections has increased over the past 10-12 years, which is associated with both an increase in the incidence of HIV infection and an increase in recorded cases. One of the most important risk factors for the occurrence of HIV-associated deep mycoses is the immunodeficiency state and the likelihood of developing severe clinical forms of the disease is determined by the severity of immunodeficiency. Among HIV-associated deep mycoses in patients with deep immunodeficiency, the infection caused by Cryptococcus neoformans often began to be recorded [1]. Cryptococcosis is recognized as the second most important mycotic infection. HIV-associated cryptococcal infection is detected with unequal frequency in different regions of the world: in Europe - 2-4%, in America - 30%. According to F. Odds (2009), in the world they annually sick from 700 thousand to 1 million people. And according to the Center for Disease Control (CDC, USA), about 1 million cases of cryptococcosis in HIV-infected patients are registered annually in the world [1]. According to large retrospective studies of HIV-infected patients, cryptococcosis occurs from 1.85% in Russia to 9.1% in the United States[8]. In economically developed countries, the cryptococcosis incidence is 30–66 cases per 1 million people per year [2]. Cryptococcal infection occurs mainly in patients with T-cell immunodeficiency and is characterized by frequent damage to the central nervous system. Quite often, cryptococcosis is the first AIDS stage manifestation. This figure varies from 39% in the United States (1992-2000) and 41.7% in Tunisia (1991-2000) to 58.8% in France (after the mid-90s) and 67.2% in Italy (1985-1999).

One of the most common forms is a cryptococcal infection caused by Cryptococcus neoformans (Sanfelice) Vuillemin (1901), especially C. neoformans var. neoformans, less commonly C. neoformans var. Gatii. [3]. The main causative agent of cryptococcosis is Cryptococcus neoformans, less commonly the disease is caused by C. Laurentii and C. Albidus. Pathogenic C. neoformans strains have a pronounced neurotropism, so the clinical cryptococcosis forms in most cases end in damage to the brain and its membranes [9]. A disease feature is the clinical manifestations severity and a very high mortality rate. During the initial therapy period, 10–25% of patients die, another 30–60% die within the next 12 months [6]. Mortality from cryptococcosis in the United States is 12%, and in Africa - 75–90%. The highest frequency of deaths from cryptococcal infection in HIV-infected patients was observed before the introduction of highly active antiretroviral therapy. With cryptococcal meningoencephalitis in HIV-infected untreated patients, it reaches 100%. Without HIV infection specific treatment, with a decrease in CD-4 lymphocytes of less than 100 cells/mm^3, the cryptococcosis incidence is from 4 to 30% and significantly decreases with the early ART prescription [2]. The main diagnostic method for cryptococcal infection is the cryptococci detection with microscopy and/or culture in the study of CSF, blood, and other substrates. Cultural diagnosis is considered the "gold standard" in diagnosis. In this case, the growth of colonies appears on the 3rd - 15th day, and it is difficult to isolate a pure culture of C. neoformans: it is known that pathogens of fungal infections are present in various mycoassociations in samples of clinical material, especially in HIV-infected patients. However, in terms of growth quality, yeast-like fungi are often ahead of mold fungi and it is much more difficult to isolate micromycetes of the genus Cryptococcus in culture compared to Candida sp. Determination of Cryptococcus neoformans antigen in cerebrospinal fluid, blood by latex agglutination test, which according to published data is found in 90% of patients, is still problematic due to the lack of available test systems[3]. Antibodies to the pathogen in blood serum are detected only in one third of patients with cryptococcal meningitis and are sometimes present in the serum of healthy people. Therefore, at present, the microscopic examination of cerebrospinal fluid remains the simplest and most informative laboratory method in the diagnosis of cryptococcosis [4]. According to the literature, the most severe course of disease generalized cryptococcosis forms have[13]. During the initial period of therapy, 10–25% of patients die, another 30–60% over the next 12 months. [14]. In this regard, there is an urgent need for early diagnosis and intensive care of cryptococcosis. The clinical manifestations of cryptococcosis are nonspecific and depend on the localization of the process. The most common clinical signs are febrile body temperature, persistent headache, dizziness, impaired consciousness, less commonly coughing, shortness of breath, rashes on the skin. In many clinical trials with cryptococcal meningitis or meningoencephalitis, about 75% of researchers have noted cases of high intracranial pressure caused by a rapid increase in cerebrospinal fluid [14]. The most characteristic development of subacute meningitis. In some patients, the disease is asymptomatic. Often with a cryptococcal lesion, a disorder of consciousness develops, visual acuity decreases, focal symptoms appear in the form of hemiparesis, ataxia, damage to the cranial nerves. The main feature of the cryptococcal meningitis clinical manifestations, according to a literature review, is negative meningeal symptoms, it is extremely rare for a patient to be clearly positive[11]. Mental disorders were noted in the form of decreased memory, uncriticality, euphoria, depression, changes in personality characteristics and even signs of deep encephalopathy[4]. The disseminated clinical forms of cryptococcal mycosis in HIV-infected people include damage to many organs and systems, especially the membranes of the brain (cryptococcal meningoencephalitis occurs in 80% of cases), as well as the heart, bones, kidneys and adrenal glands, eyes, prostate gland and lymph nodes[3]. Of particular scientific and practical interest are cases of generalized cryptococcosis forms with disseminated damage to almost all organs and tissues. In these situations, deep multiple organ dysfunction often leads to death until the moment when the attending physician can identify unfavorable background mycosis conditions in the form of various variants of immunological insufficiency [1].

Rare non-meningeal forms of infection include damage to the lungs, skin, joints, eyes, adrenal glands, gastrointestinal tract, liver, pancreas, prostate and urinary tract. Skin lesions with disseminated infection are found in 10-15% of HIV-infected patients with cryptococcosis [7].

Clinical guidelines for the treatment of cryptococcal meningitis currently need to be reviewed. The standard of combination of amphotericin B deoxycholate (amphotericin B deoxycholate, amphoto-B) and flucytosine (flucytosine) adopted in developed countries

is not acceptable in low- and middle-income countries, due to the high cost of flucytosine. For this reason, the combination of amphotericin-B and fluconazole (fluconazole) is of interest. According to the literature, antagonism is possible theoretically and in vitro between these antifungal drugs [10]. Such a combination was used for the early treatment of cryptococcal meningitis by an international team of scientists led by Dr. Peter G. Pappas from the University of Alabama, USA. The authors convincingly showed that the early combination treatment of cryptococcal meningitis with amphotericin B and fluconazole is well tolerated, and when using high-dose (800 mg per day) fluconazole also improves the results. In an accompanying editorial, Dr. Harrison T.S. from St.George University in London notes that the worst results in the low-dose fluconazole group could be due to the antagonism between amphotericin B and fluconazole [10]. Using the currently recommended treatment method based on Amphotericin[15], the clinical course of the disease in those who survive is often complicated by a prolonged or recurrent disease. There are unexplored clinical, virologic, immunological aspects of HIV-associated cryptococcosis[4]. The comparative rarity of the lesion multiple nature, the lack of objective clinical and laboratory data allowing to suspect and confirm cryptococcal infection with HIV in a timely manner, lead to errors in making a timely diagnosis, which entails errors in the initial pathogenetic treatment[6].

The question remains open whether prescribing antiretroviral therapy (ART) is possible and necessary shortly after diagnosis of cryptococcal etiology. In the literature, there is only evidence that an antiretroviral drug from the group of protease inhibitors indinavir restrains capsule formation in vitro[14]. The higher thickness of the capsule in patients receiving ART than in patients who have not received therapy or received only antimycotics, is probably associated either with the therapy ineffectiveness or with the fact that the capsule is not only a virulence factor but also protects cryptococcus from the macroorganism[16]. Another major concern for doctors is the of Immune Reconstitution Syndrome (IRIS) development. Quite often, cryptococcosis develops as a primary opportunistic infection against the background of an inflammatory immune system restoration syndrome. IRIS occurs in 15–20% of individuals who develop cryptococcosis initially and only then start ART, which leads to relapse and a more severe clinical course of the disease[15]. The development of more effective prevention/treatment method, as well as ensuring a safe and quick ART start, and its effectiveness in the treatment of antimycotic drugs, is important and is one of the main components of improving the HIV-associated cryptococcosis outcomes in patients. By the present date, the timing of antiretroviral therapy start remains uncertain[17].

Aim of Research: The main objective of this research is to study the prevalence of HIV-associated, identifying the clinical and laboratory cryptococcosis manifestations associated with inflammatory immune restoration syndrome in Uzbekistan.

Materials and Method

To achieve the aim and solve the tasks in the work, a general scientific methodology was used, based on an integrated systematic approach using epidemiological, clinical, microbiological, molecular genetic and statistical method. The prevalence of cryptococcosis in HIV-infected people in Uzbekistan was studied based on statistics from the Republican AIDS Center from 2012 to 2018. A screening method was performed by rapid tests for the presence of C. neoformans antigen in 347 naive adults living with HIV with a CD4 level of ≤100 lymphocytes in quick tests. The immune system state was studied by the total number of T-lymphocytes and their subpopulations in accordance with the differentiation clusters CD3 +, CD4 + and CD8 + lymphocytes using a Partec Cy FLOW Counter cytofluorimeter. HIV virus nucleic acids were detected by the Polymerase Chain Reaction method on a Rotor Gene 6000 TM. The diagnosis was made according to the EORTC/MSG (Europen Organization for Research and Treatment of Cancer/Mucoses Stady Group) criteria based on positive results by the rapid testing method for the presence of CrAg, as well as the determination of the pathogen C. neoformans in a microspy smear stained with Indian ink and culture growth on the Saburo environment. From instrumental research method, a computer tomogram of the brain, lungs, and X-ray examination of the upper and lower respiratory tract were also performed. A retrospective and prospective analysis of the clinical manifestations of 347 outpatient records and medical records was performed. The results of antifungal and antiretroviral therapy were evaluated in 37 patients with HIV-associated cryptococcal meningitis and meningoencephalitis who were hospitalized at the clinic of the Research Institute of Virology and the Specialized Infectious Diseases Hospital and at the Ust'-Izhora

Clinic, St. Petersburg, Russian Federation; then they were observed on an outpatient basis in dispensary departments of the RC AIDS, 14 regional AIDS centers. The research period is from 2012 to 2018. The criteria for selecting patients for the 1st (main) group were: cryptococcal meningoencephalitis and meningitis; adherence to ART and its beginning (no more than 6 months); positive immunological and virologic response to ART with the development of a clinical worsening of the condition with meningeal symptoms. The control group included 17 patients with HIV-associated cryptococcal meningoencephalitis and 20 patients in the main group with HIV-associated cryptococcal meningoencephalitis and meningitis taking ART antiretroviral therapy for a period of 1 to 12 months. The age index of the 1st and 2nd study groups ranged from 19 to 53 years (average 26.3±2.3 years, 83% of men).

Results

According to the research results, the cryptococcosis frequency in HIV-infected patients according to the long-term statistics of the Republican AIDS Center (from 2012 to 2018) amounted to 3.9% of HIV-infected patients with opportunistic diseases. Potential factors for the cryptococcosis development have been studied. Conducted in the case-control study. As hypothetical risk factors for the development of cryptococcosis in HIV-infected people, we included medical factors (HIV infection and its duration, the presence of chronic diseases of the upper respiratory tract, chronic hepatitis C, tuberculosis, diabetes mellitus, frequent hospital treatment, severe immunodeficiency of the patient, the development and presence of the clinical stages of HIV infection), as well as "social and behavioral" (employment, living conditions, being in a penitentiary institution, dependence on psychoactive substances, as well as socio-demographic risk factors for the development of the disease. In the group "case" 37 patients were included with a confirmed cryptococcosis diagnosis and the control group consisted of 23 patients without cryptococcosis who were observed in the same AIDS center or clinic at the same time. The groups were comparable by sex, age, territory of residence, stage of HIV infection, the number of CD4 < 100 cells/μl of lymphocytes, absent or taking ART.

The study revealed that cryptococcosis is significantly more likely to occur in HIV-infected patients living in private uncomfortable homes, where access to clean drinking water was difficult and there was no sewage. A direct relationship was found between the cryptococcosis occurrence and the active use of narcotic substances. The likelihood of developing cryptococcosis was also determined by the severity of immunodeficiency. The duration of HIV infection, a low level of limocytes (CD4≤100), previous hospitalizations created favorable conditions and created a high level of cryptococcal infection risk. The results obtained showed a direct relationship between these signs and the likelihood of developing cryptococcosis (OS 2.659 and 3.711; CI = 1.335-9.517). When examining 347 HIV-infected patients, a low level of limocytes (CD4≤100), serum antigenemia was detected in 11.2%. In 4.3% of patients, high titers were determined (≥1: 1024). High titers of the pathogen subsequently were a marker of poor prognosis. The research determined the time from the onset of symptoms to diagnosis on average 24.5 days passed (from 14-80 days). Cryptococcosis is rarely the only opportunistic infection in HIV-infected patients. Often combined with candidiasis (68% and 59%), cytomegalovirus infection (1.7% and 1.2%), and tuberculosis (17.2% and 15.3%). Severe intoxication and cerebral symptoms in cryptococcal meningoencephalitis were noted in 63% of patients of the first and second groups. Tachycardia (heart rate 88-104 per minute), hypotension (from 100/60 to 80/50 mm Hg), dyspnea (BH 22-38 per minute) were recorded in 48% of the 1st group and 52% of cases in 2nd group of patients. In our study, only 3 patients of the 2nd group and one patient of the 1st group were diagnosed within the first 14-18 days from the start of the disease. Upon admission, all patients complained of severe headache in the frontal and temporal areas, the average duration of which was 14-16 days in both groups. Irritability, nausea, vomiting, dizziness, unstable gait were observed in 47% of patients of the 1st group and 54% of the 2nd group of patients. Visual impairment (double vision) was noted in 5.4% of patients of the 2nd group. In the 1st group of patients, body temperature rose to 38–40°C and remained with the wrong type of temperature curve (88.4±3.21 cases) from 18 to 32 days, weakness (84±3.83), persistent generalized lymphadenopathy (44±4.23), sleep disturbances (87.5±4.11). Arthralgia disturbed 19.7±4.32 patients. Respiratory tract lesions with oropharyngeal mycoses were predominant among group 1 patients, and showed a productive cough in 77.5±3.97 cases (versus 48±3.87 in group 2 patients) and shortness of breath in 67.5±3, 7 cases (versus 24.3±3.45 in patients of the 2nd group). 45% of patients of the 1st group and 27% of patients of the 2nd group showed meningeal symptoms. Focal

symptoms (hemiplegia, nystagmus, anisocoria) were observed in 12.5±3.1 patients of the 1st group and in 7.3±3.7 patients of the 2nd group. Patients were depleted, the skin was pale, marked peeling of the skin in both groups was noted. Peripheral lymph nodes are enlarged to 1 cm, dense, painless. Tachycardia (heart rate 88–104 per min), hypotension (from 90/60 to 80/50 mm Hg), shortness of breath (BH 22–38 per min) were noted. Hypochromic anemia with erythrocyte counts from 2.3 to 3.3×10/12/L, leukopenia from 1.5 to 3.9×10/9/L, shift of the formula to the left (relative neutrophilia), lymphopenia were found in the hemogram in patients with hypochromic anemia from 3 to 7% and high ESR (39–66 mm/h). The number of CD-4 lymphocytes in the blood ranged from 7 to 86 cells/μl. The viral load was 131,000–634,000 copies of HIV RNA in 1ml of blood in the 1st group and 723,000–1,232,000 copies of HIV RNA in 1ml of blood in the 2nd group. Magnetic resonance imaging (MRI) revealed hydrocephalus, arachnoid changes in the cerebrospinal fluid. In patients of the 1st group revealed multiple nodes in the parenchyma of the brain, meninges, basal ganglia and midbrain. In patients of the 1st and 2nd group, cortical atrophy was observed. With repeated MRI performed in 3 patients of the 2nd group after 9-14 days, structural disorders of the basal nuclei of the white matter of the cerebral hemispheres, signs of focal encephalitis appeared.

For diagnostic purposes, all patients underwent puncture of the cerebrospinal fluid (CSF). The results of CSF tests showed a sharp increase in cerebrospinal fluid pressure (190-450 mm water column). Liquor is transparent. Microscopically in the cerebrospinal fluid, mainly lymphocytic cytosis was observed (from 12 to 1824 cells/μl), the protein content was increased (450-1400 mg/l), and glucose was reduced (0.1-2.5 mmol/l). The number of leukocytes in the CSF in 4 patients of the 2nd group was normal. The causative agent was detected by CSF microscopy in 89.1% of patients in both groups. Repeated adequate correction of intracranial hypertension using spinal puncture was performed in 53% of cases of the 1st group and 33% of cases of the 2nd group. Considering that in 5 patients with a three-time study of CSF with a different time interval (from 1 to 3 months), the pathogen was determined, resistance studies were performed in connection with long-term fluconazole therapy. An analysis was made of the IRIS effect on the following factors development: quantitative characteristics of CSF culture, initial CD4 lymphocyte count and viral load before ART, pressure during spinal puncture, leukocytes levels, protein, glucose in CSF.

Cultural diagnosis was performed using standard Saburo medium. Colonies of Cryptococcus neoformans were usually seeded after 48–72 hours. At the same time, cryptococcus was determined microscopically in 70%, culture was isolated in 77%, which made it difficult to evaluate the antimycotic therapy effectiveness in 23% of patients. Obtaining a cryptococcus culture made it possible to determine the sensitivity of the isolated strain to antifungal drugs. The sensitivity of the pathogen during the initial CSF study was 93±3.9 in the 1st group, and 91.2±3.7 in the 2ndgroup to amphotericin B; 89±3.9 in the 1stgroup, and 73±3. 9 in the 2ndgroup to fluconazole. The combination of these drugs was used as an etiotropic treatment in accordance with international recommendations. We used doses of amphotericin B at 0.7–1 mg/kg/day and fluconazole at doses of 800 mg/day, as recommended in modern guidelines. Fluconazole inhibits the synthesis of ergosterol in fungi, has excellent absorption and penetration into the CSF, and is a less toxic drug compared to amphotericin B. This treatment regimen allowed us to more quickly get the initial antifungal effect and the possibility of avoiding the toxicity of amphotericin B considering the therapy duration. Headache disappearance by the 7th day of antifungal therapy was observed in 12% against 18% of the 1st and 2nd groups of patients, and by the 14th day in 69% and 48% of the 1st and 2nd groups of patients. Treatment was considered successful if cerebrospinal fluid cultures were negative after 2 and 10 weeks, or if positive disease dynamics were observed in patients after 2 weeks and no symptoms after 10 weeks. Cryptococcus in CSF was determined by PCR in 31 cases. Before treatment, the microbial load ranged from 17,700 to 6,456,700 copies in 1 μl. During treatment, there was a decrease in load from undetectable values to 2,900 in the 1st group of patients and up to 12.348 copies in the 2nd group. Despite the ongoing therapy, 3 patients (1 from the 1st group and 2 from the 2nd group) did not observe treatment efficacy and the disease continued to progress. These patients in the consolidated phase of treatment switched to introconazole for 8-10 weeks of treatment. After 5–9 days of the consolidated treatment phase, 2 patients experienced deterioration of health, signs of respiratory and cardiovascular failure, cerebral coma developed, which resulted in death on the 42–48th day of the disease. The overall mortality rate was 5%-5.2% of cases, with no significant difference between the groups. The average number of CD4 lymphocyte cells

among patients of the 1st group at the time of diagnosis was 13.7±3.27 cells/μl, while in the 2nd group it was two times or higher (28.1±3, 23 cells/μl). By the 3rd month of specific treatment of cryptococcus, the number of CD4 increased to 56.3±3.7 cells/μl in the 1st group and to 78±3.2 cells/μl in the 2nd group. Patients of the 1st group during the prevention of relapse of the disease for 2-3 months, was prescribed antiretroviral therapy. In the 2nd group of patients, the average number of CD4 cells at 6 months after initiation of ART was 73±3.24 cells/μl, in patients of the 1st group for this period the number of CD4 cells was 103±3.78 cells/μl. HIV RNA in plasma was not detected (i.e., <400 copies/ml) in 8 (44%) patients of the 2nd group and in 15 (83%) of the 1st group at 6 months of ART. The data showed that patients in whom IRIS manifested with cryptococcal meningoencephalitis, had a significantly faster start and more progressive severe course. But the response to treatment with antifungal drugs on the background of ART was faster in the 2nd group.

Discussion

Thus, the cryptococcosis frequency in HIV-infected patients in Uzbekistan was first determined. The low rates of cryptococcosis among HIV-infected people in Uzbekistan are noteworthy. It amounted to 3.9% of HIV-infected patients with opportunistic diseases. This may be due to insufficient quality of diagnosis. For the first time, "medical" and socio-demographic risk factors for the cryptococcosis development in HIV-infected patients were identified. The most significant combinations of risk factors were the combination of the no employment with the fact of frequent hospitalization in hospitals, the lack of supportive prevention of the disease (in 32.6±5.99%), poor social conditions (in 13.7±4.27%) examined in the group observations. The results of the study confirm the direct relationship between the degree of immunodeficiency in HIV infection and the occurrence of cryptococcosis. The disease significantly more often develops with a CD4 T-cell count of ≤100 cells/μl. Also, the importance of the absolute number of leukocytes and lymphocytes in the peripheral blood was revealed, with their reduction, the risk of cryptococcosis in HIV-infected patients significantly increases. The results of the study also confirm the need for rapid testing for CrAg and fluconazole prophylaxis for cryptococcal disease in patients with CD4≤100 lymphocytes. The results of the study are consistent with the literature that cryptococcosis occurs against the background of severe insufficiency of cellular immunity. Therefore, screening with rapid tests for detecting CrAg in all HIV-infected patients with a CD4 level of ≤100 is necessary. The low information content of the specific clinical picture of the disease requires doctors when neurological symptoms appear, and requires microscopic examination of CSF in patients with prolonged persistent headache, even in the absence of meningeal symptoms. Cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis since the clinical features are not specific. In our studies, the typical clinical cryptococcosis manifestations in HIV-infected patients were an acute and chronic process development with high fever, a manifest clinical picture of CNS damage in the form of meningoencephalitis. The specific features of the course of cryptococcal meningoencephalitis in HIV-infected patients is the development of a manifest CNS lesion in the absence of clinical signs of disturbance on the part of the internal organs. The disease is characterized by a severe course in 92.6±5.99% of cases. It should be noted that most patients observed by us (83.0±3.72) had meningeal symptoms, although according to the literature, they are found only in 30.0% of patients suffering from cryptococcosis. None of the patients observed by us in vivo revealed clinical symptoms of lesions of the skin and other internal organs characteristic of a generalized pathological process. However, when conducting mycological studies revealed the presence of C. neoformans in cerebrospinal fluid in all patients of both observation groups. Uncharacteristic changes were CSF. The most demonstrative was an increase in protein from 0.47 to 4.84 g/l in 88% of patients, which indicated an increase in the permeability of the blood-brain barrier. There was also a decrease in glucose from 0.47 to 2.1 mmol/l in 36% of patients. 57% had lymphocytic or mixed pleocytosis ranging from 12 to 293 cells/μl, which indicated a weak inflammatory reaction. Liquor hypertension did not play a significant role in the severity of the course of the disease in both study groups. Increased attention is required not only to the patient's condition, but also to microbiological CSF monitoring with determination of the pathogen sensitivity during treatment. This will allow timely determination of the possible resistance formation to antifungal drugs. Adequate antimycotic therapy performed in the early days determined the positive dynamics of the pathological process.

An early assessment of treatment results (on days 10-14) is possible based on mycological CSF examination and a decrease in the microbial load determined by PCR (decrease after 2 weeks by 10 thousand times).

Maintenance therapy based on fluconazole (200 mg/day) with poor adherence or early cessation of treatment can lead to relapse of cryptococcal meningitis, which was noted in patients of the 1st group (84±4.7). Itraconazole was used as rescue therapy in 3 cases of fluconazole resistance.

Another aggravating factor in the disease development was the significantly expressed degree of immunosuppression (CD4≤100 cells/μl) in the observed patients. An increase in the content of CD4 + cells to a greater degree in patients with HIV-associated cryptococcal meningoencephalitis during ART contributed to faster and more successful treatment, and vice versa, the late ART start in patients with low CD4 counts increases the risk of cryptococcosis and other opportunistic diseases. But despite the increase in the absolute amounts of CD4 + lymphocytes in the main group, the fact is obvious that an increase in their number does not yet prove the normalization of the immune response lost in the early stages of HIV infection. The presentresearch once again shows that antifungal treatment with antiretroviral drugs helps to restore CD4 cell levels more quickly, as well as preventing the inflammatory immunity syndrome development, which can lead to severe cases of generalized forms.

Conclusions

1. It was found that the cryptococcosis frequency in HIV-infected patients was 3.9% of HIV-infected patients with opportunistic diseases.
2. Among the risk factors for the development of cryptococcosis in HIV-infected patients of the main group were socio-demographic (no employment, unsatisfactory housing and utilities) and medical (frequent hospitalization, lack of maintenance prophylaxis with fluconazole). The combination of these factors was the most significant.
3. The presence of a direct relationship between the degree of immunodeficiency in HIV infection and the cryptococcosis occurrence has been determined. The disease significantly more often develops with a CD4 T-cell count of ≤100 cells/μl.
4. The low information content of the specific clinical picture of the disease dictates the need for routine rapid testing for CrAg and fluconazole prophylaxis for cryptococcal disease in patients with CD4≤100 lymphocytes.
5. Cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis since the clinical features are not specific.
6. Characteristic changes in the CSF in cryptococcal meningoencephalitis were an increase in protein, a decrease in glucose levels, without much difference in the compared groups.
7. Microbiological CSF control and monitoring with determining the pathogen sensitivity during treatment allowed to timely determine the resistance formation to antifungal drugs.
8. Antifungal treatment on the background of antiretroviral drugs contributes to a more rapid increase in the level of CD4 cells.

Ethical Clearance: No ethical approval is needed.

Source of Funding: Self

Conflict of Interest: Nil

References

1. Cryptococcal Meningitis TBTS. Harrison British Medical Bulletin. 2004; 72(1): p. 99-118.
2. N.P. Elinov IAB/Zpmm. Elinov, N.P. The past and present of Cryptococcus neoformans (Sanfelice) Vuillemin (1901) as an object of study of a potentially formidable pathogen for humans. 2006; 8(2): p. 47-51.
3. Khodunova E.E. FIN, PENea. Cryptococcosis in hematological practice. Therapeutic archive. 2003; 11: p. 41-46.
4. Klimko, N.N. Mycoses: diagnosis and treatment: a guide for doctors/N.N. Klimko. 2007;: p. 336.
5. A.M. Konstantinova VAZ. Konstantinova, A.M. Pathological anatomy of cryptococcal brain damage in HIV-infected patients. HIV infection and immunosuppression. 2010; 2: p. 113-117.
6. micol AMK/Zpm. Konstantinova, A.M. Pathomorphological and mycological analysis of cryptococcosis in experiment and on autopsy material for HIV infection. 2010; 12(4): p. 42-47.
7. V.S. Lessovoy AVL/Zpmm. Lessovoy, V.S. Mycosis of the central nervous system (review). 2008; 10(1): p. 3-6.

8. Monari C. PE, BGea. Influence of Indinavir on virulence and growth of Cryptococcus neoformans//J. Infec. Dis. 2005; 191: p. 307-311.
9. Andrew Kambugu DBMJRMOENJARRMRKHMKMASPRBaDRB. Outcomes of Cryptococcal Meningitis in Uganda Before and After the Availability of Highly Active Antiretroviral Therapy. Clinical Infectious Diseases. 2008; 46: p. 1694-1701.
10. phase PPeaA. randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis. 2009 JUN; 48(12): p. 1775-83.
11. A.G. Rakhmanova YVLEVS/Zpmm. Rakhmanova, A.G. The proportion of mycoses in the structure of secondary diseases in patients with HIV/AIDS. 2004; 6(1): p. 9-12.
12. Senior, K. Do we need to pay more attention to cryptococci? K. Senior//The Lancet Infectious Diseases. Russian edition. 2010; 1(5): p. 286-288.
13. Tihana Bicanic ea. Immune Reconstitution Inflammatory Syndrome in HIV-Associated Cryptococcal Meningitis: A Prospective Study. J Acquir Immune Defic Syndr. 2009; 51: p. 130-34.
14. Bicanic T, Meintjes G, Rebe K, Williams A, Loyse A, Wood R, et al. .
15. micol NVV/Zpm. Vasilieva, N.V. Cryptococci and cryptococcosis at the present stage. 2002; 4(2): p. 45-46.
16. Vengerov Yu. Ya. VOE, SAP, STS, VAS, MMN, MNN. Clinic and diagnosis of cryptococcal meningoencephalitis in patients with HIV infection. Materials of the V Annual All-Russian Congress on Infectious Diseases. 2013;: p. 85.
17. V.A. Zinserling MLCAMK. Zinserling, V.A. Cryptococcosis. Infectious lesions of the central nervous system: issues of etiology, pathogenesis and diagnosis: a guide for doctors. 2011;: p. 509-515.