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İNSAN İMMUNODEFİSİTİ VİRUSUNA YOLUXMUŞ XƏSTƏLƏRDƏ TOKSOPLAZMOZ ENSEFALİTİNİN GEDİŞATININ KLİNİK XÜSUSİYYƏTLƏRİ

T.A.Vəliyeva¹, E.İ.Bodnya¹, V.D.Makarenko¹, V.V.Pavliy², İ.V.Kroxmal³¹Xarkov Milli Tibb Universiteti diplomdan sonrakı Təhsil və Elm İnstitutunun İnfeksiyon və Uşaq İnfeksiyon Xəstəlikləri, Parazitologiya, Ftiziatriya və Pulmonologiya kafedrası,²Xarkov Milli Tibb Universitetinin diplomdan sonrakı Təhsil və Elm İnstitutunun Dermatovenerologiya və Cərrahi Dermatologiya kafedrası,³Klinik Regional Xəstəxananın Uşaq İnfeksiyon Xəstəlikləri şöbəsi, Xarkov, Ukrayna

Xülasə. Məqalədə HIV-ə yoluxmuş 23 xəstədə toksoplazmoz ensefalitinin (TE) klinik xüsusiyyətləri və müayinələrin nəticələrinin retrospektiv analizi təqdim edilmişdir. Pasiyentlərdən 11 nəfər (47,8%) kişi, 12 nəfər (52,2%) qadın, yaşı 31-dən 55-ə qədər (orta yaş isə $37,5 \pm 0,38$ il) olmuşdur. Xəstələrin periferik qadında CD4+ limfositlərinin orta sayı $102,5 \pm 21,2$ hüceyrə/mkl, diaqnoz qoyulduqda isə plazmadakı HIV RNT yükü orta hesabla $292773,8 \pm 113180$ /ml idi. Bütün xəstələrdə HIV infeksiyasının 4-cü mərhələsi (CDC təsnifatına görə, 1993) təsdiq edilmişdir. Toksoplazmoz infeksiyası qanın seroloji analizində (ELISA metodu üzrə toksoplazmaya qarşı IgG anticisimciklərinin olması) ilə təsdiqlənmiş, toksoplazmoz ensefalitinin isə MRT zamanı beyində xarakterik müşahidələrdən aydın olmuşdur ki, dəyişikliklərə görə təsdiqlənmişdir. HIVə yoluxmuş xəstələrdə toksoplazmoz ensefalitinin diaqnozu tədricən inkişaf edir və xəstəliyin ilkin təzahürləri kimi idrak və psixi pozuntular özünü göstərir, daha sonra isə lokal nevroloji pozuntular (hemiparezlər, qıcolmalar, nitq problemləri) təzahür edir. Xəstəliyin başlanğıcında toksoplazmaoz diaqnozu təsdiqlənmiş bütün HIV xəstələri toksoplazmoz ensefalitinin inkişaf riski qrupuna daxil edilə bilər. CD4+ hüceyrələrinin səviyyəsi 200 hüceyrə/mkl-dən aşağı düşdükdə toksoplazmoz ensefaliti (TE) və bu, çoxsaylı simptomlarla xarakterizə olunur. Tədqiqatdan aydın olmuşdur ki, HIV-ə yoluxmuş xəstələrdə TE-nin inkişafı zamanı beyin əlamətlərinin müxtəlifliyi toksoplazmoz infeksiyasının ağırlıq dərəcəsi, aktivliyindən və müddətindən asılıdır.

Açar sözlər: toksoplazmoz ensefaliti, HIV infeksiyası, kliniki xüsusiyyətlər**Ключевые слова:** токсоплазмозный энцефалит, ВИЧ инфекция, клинические особенности**Key words:** toxoplasmic encephalitis, HIV infection, clinical features

FEATURES OF THE COURSE OF TOXOPLASMIC ENCEPHALITIS IN HIV-INFECTED PATIENTS

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This article presents the results of a retrospective analysis of clinical characteristics and examination outcomes in 23 patients with toxoplasmic encephalitis (TE) among HIV-infected individuals. Among the examined individuals, 11 (47.8%) were men and 12 (52.2%) were women. The patients' ages ranged from 31 to 55 years, with an average age of 37.5 ± 0.38 years. The average CD4+ lymphocyte count was 102.5 ± 21.2 cells/ μ l, and the HIV RNA load in plasma was $292,773.8 \pm 113,180$ copies/mL. All patients were confirmed to have stage 4 HIV infection (according to the CDC classification, 1993). Toxoplasmosis infection was confirmed by blood serology (presence of anti-Toxoplasma IgG antibodies via ELISA), and toxoplasmic encephalitis was diagnosed through MRI with characteristic focal brain changes. According to

our analysis toxoplasmic encephalitis in HIV-infected patients develops gradually, with cognitive and psychiatric disorders as primary manifestations, followed by focal neurological impairments (hemiparesis, seizures, speech problems). All HIV patients with detected Toxoplasma antibodies at the onset of the disease can be considered at risk for developing toxoplasmic encephalitis. TE in the brain manifests when CD4+ cell levels drop below 200 cells/ μ L and is characterized by polysymptomatic presentation, with an average of 5.67 ± 0.37 symptoms in our patients. The data from our correlation analysis between altered blood parameters and the presence of symptoms in TE among HIV-infected patients showed that the greater the severity, activity, and duration of toxoplasmic infection (indicated by eosinophilia), the more diverse the symptoms. This, in turn, leads to an increase in ESR, the development of leukocytopenia, and hypochromic anemia.

Toxoplasmosis is a global problem since *Toxoplasma gondii* (*T. gondii*) is widespread worldwide [1,2]. Toxoplasmosis is caused by the intracellular parasite *T. gondii*. It is a unicellular organism that belongs to the type (*Apicomplexa*) [3]. The definitive hosts of *T. gondii* are felines, in whose intestines the parasite reproduces sexually, forming oocysts that are then excreted into the environment with feces and can remain infectious for a long time in the external environment [4,5]. Infection enters the human body after consuming food or water contaminated with oocysts or through eating the meat of infected animals containing tissue cysts of the parasite [6]. After entering the body, *T. gondii* spreads through the blood and lymph nodes [7]. In healthy individuals, the immune system usually controls the infection, keeping the parasite in a latent state. However, in cases of immunodeficiency (such as in HIV-infected individuals), the parasite is reactivated, which can lead to serious conditions such as toxoplasmic encephalitis [8,9].

According to studies, up to 30-40% of HIV-infected individuals who do not receive toxoplasmosis prophylaxis or antiretroviral therapy (ART) are at risk of developing this complication [10,11].

Toxoplasmic encephalitis (TE) is a serious and dangerous opportunistic disease in HIV-infected patients, characterized by a severe progressive course and high mortality in the absence of treatment [12,13]. Decreased immunity in HIV-infected patients, especially when CD4 lymphocyte counts drop below 200 cells/ μ L, promotes reactivation of latent *T. gondii* infection, leading to central nervous system (CNS) damage [14].

TE is a global health problem, especially in countries with high levels of HIV infection and limited access to ART [15,16]. In

Ukraine, where HIV infection remains a significant problem, TE has high clinical relevance. Despite the lack of precise statistical data, there are concerns that the disease may be underestimated or not diagnosed in time [17].

The purpose. To analyze the peculiarities of the course of TE in HIV-infected patients.

Materials and methods. A retrospective analysis of the clinical manifestations and examination results of toxoplasmic encephalitis in 23 HIV-infected patients who were hospitalized at the Kharkiv Regional Infectious Diseases Clinical Hospital from 2018 to 2023 was conducted. The inclusion criteria for the analysis were the presence of TE in HIV-infected patients and the exclusion of other opportunistic diseases. Among the 23 HIV-infected patients with TE, 11 (47.8%) were men and 12 (52.2%) were women. The age of the patients ranged from 31 to 55 years, with an average of 37.5 ± 0.38 years. Sexual transmission was the route of infection in 10 (43.5%) patients, while 10 (43.5%) were infected parenterally (through the use of contaminated narcotic substances). Three patients (13.0%) could not identify the source of infection as they denied drug use or casual sexual encounters.

In three cases (13.0%), HIV infection was first diagnosed during hospitalization at the stage of disease manifestation, while the remaining 20 (87.0%) patients have been suffering from HIV infection for 5-6 years. All patients underwent identification testing for HIV antibodies using the standard enzyme-linked immunosorbent assay (ELISA). Blood tests for HIV were positive in all patients, with the disease in the 4th stage (according to the CDC classification, 1993). The presence of specific antibodies to toxoplasmosis was determined by serological blood testing using ELISA. Antibodies IgG to *T. gondii* were detected in 20 (87.0%) patients, and IgM and IgA antibodies were found in 5 (21.7%) patients, indicating an acute and active toxoplasmosis process. All patients underwent PCR testing of

blood and cerebrospinal fluid for *T. gondii* DNA to verify the pathogen.

Statistical analysis was performed using Microsoft Office Excel 2019. The normality of data distribution was assessed using the Shapiro-Wilk test. The mean value \pm standard error of the mean ($M\pm m$) was calculated. Correlations between variables were determined using Pearson's correlation coefficient. Differences were considered statistically significant at $p<0.05$.

Results

Upon analyzing the medical histories, it was found that 18 (78.3%) patients had not

previously received highly active antiretroviral therapy (HAART). The remaining 5 (21.7%) had been receiving it for periods ranging from 5 months to 5 years.

CD4 levels and the CD3/CD4 ratio were determined in all patients. The average CD4+ lymphocyte count was 102.5 ± 21.2 cells/ μ L, and the viral load of HIV RNA in plasma at the time of TE diagnosis was $292,773.8 \pm 113,180$ copies/mL.

Toxoplasmic encephalitis usually began gradually.

Table 1. Characteristics and frequency of complaints of TE in HIV-infected patients

Complaints	Absolute	%
General weakness	21	91,3
Headache	17	73,9
Fever	13	56,5
Weakness in the limbs	10	43,5
Nausea	8	34,8
Unsteady gait	7	30,4
Confusion or loss of consciousness	6	26,1
Decreased body weight	5	21,7
Dizziness	4	17,4
Motor aphasia (speech disturbances)	4	17,4
Difficulty concentrating or understanding text	3	13,0
Seizures	3	13,0
Double vision	2	8,7
Hearing loss	2	8,7
Memory impairment (disorientation in time and space)	2	8,7
Vision impairment	1	4,3

According to *Table 1*, all complaints can be divided into four clusters based on frequency: high, moderate, low, and very low frequency. A cluster with a high frequency of complaints includes general weakness (91.3%), headache (73.9%), and fever (56.5%). The moderate frequency cluster includes weakness in the limbs (43.5%), nausea (34.8%), unsteady gait (30.4%), confusion or loss of consciousness (26.1%), and decreased body weight (21.7%). The low-frequency complaints include dizziness (17.4%), speech disturbances (17.4%), difficulty concentrating or understanding text (13%), seizures (13%), while the very low-frequency symptoms include double vision (8.7%), hearing loss (8.7%), memory impairment (8.7%), and vision impairment (4.3%).

Among the most frequent symptom combinations (Fig.1), the first-ranking combination is general weakness and headache (73.9%). Other combinations in order of ranking include general weakness and fever (56.5%), general weakness, headache, and fever

(52.1%), headache and fever (47.8%), general weakness and weakness in the limbs (43.5%), as well as headache and weakness in the limbs (30.4%).

In relation to the total number of complaints identified in patients, the nature of their distribution curve (Fig. 2) was normal with some shift to the right, therefore, according to the form of distribution of complaints, there were 6 (23.8%), and the average value was 5.67 ± 0.37 complaints. A relatively small number of complaints (2-4) was observed in 23.7% of patients. A moderate number (5-6) was present in 38.1%, while a significant number (≥ 7) was observed in 33.4% of patients.

During objective clinical examination, 7 (30.4%) patients were in severe condition, and 16 (69.6%) were in moderate condition. Neurological examination revealed meningeal signs in 5 (21.7%) patients, hemiparesis in 14 (60.9%), and tetraparesis in 1 (4.3%) patient. Hepatomegaly was found in 11 patients (47.8%).

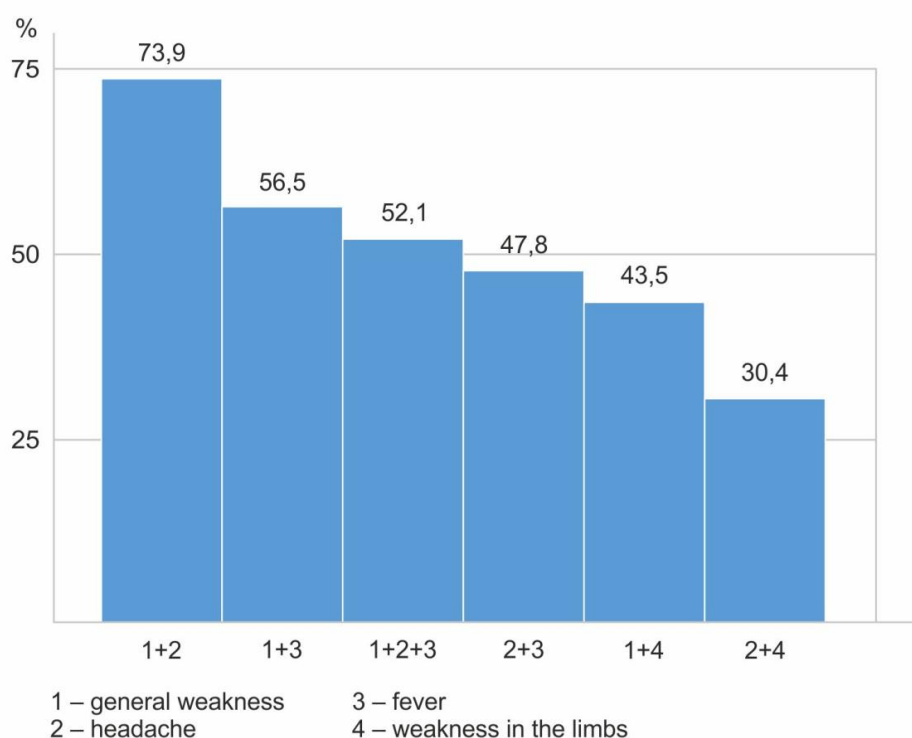


Figure 1. The most frequent combinations of symptoms in HIV-infected patients with TE

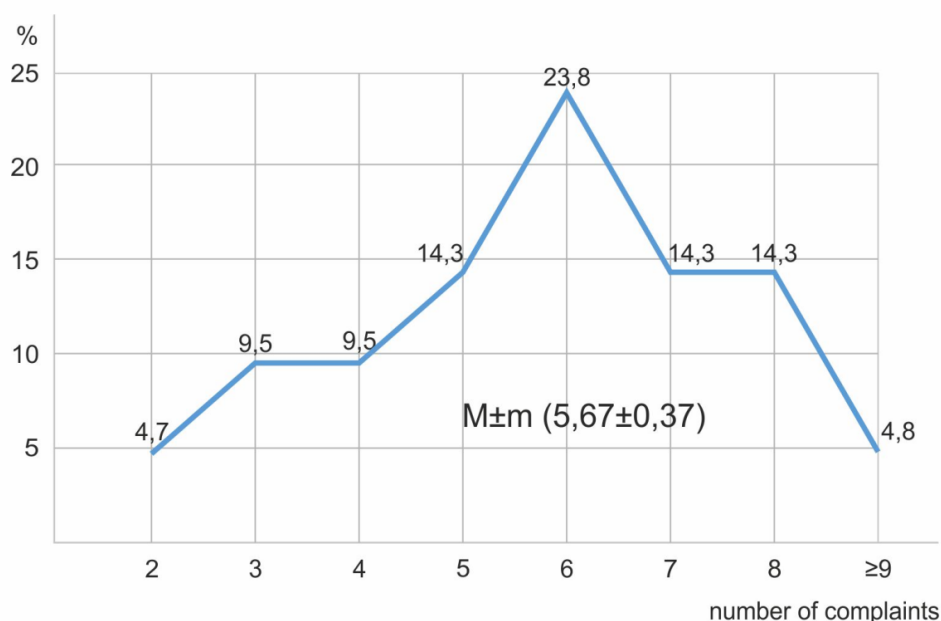


Figure 2. Distribution curve of the number of complaints of TE in HIV-infected patients

All patients underwent magnetic resonance imaging (MRI) of the brain with a contrast agent. In all cases, both hemispheres of the brain were affected, but more often (71.4%) – the right hemisphere of the cerebellum with multiple foci of annular expansion from 2 to 40 mm and perifocal edema, which indicates an infectious-inflammatory process associated with toxoplasmosis.

It should be noted that multiple lesions are typically found in toxoplasmic encephalitis, while solitary lesions are less common.

In Table 2 presents the frequency of deviations from normal blood test values. Three clusters of blood test abnormalities were identified: high, moderate, and low frequency. The high-frequency abnormalities include thrombocytopenia (78.6%), elevated ESR (73.9%), and hypochromic anemia (60.9%). The moderate frequency cluster includes lymphocytopenia (47.8%) and eosinophilia (34.8%), while the low-frequency cluster includes leukocytopenia (26.1%), lymphocytosis (21.7%), and leukocytosis (8.7%).

Table 2. Frequency of changes in blood test parameters in HIV-infected patients with toxoplasmic encephalitis

The nature of changes in clinical blood tests	Absolute	%
Thrombocytopenia	18	78,3
Increased erythrocyte sedimentation rate	17	73,9
Hypochromic anemia	14	60,9
Lymphocytopenia	11	47,8
Eosinophilia	8	34,8
Leukopenia	6	26,1
Lymphocytosis	5	21,7
Leukocytosis	2	8,7

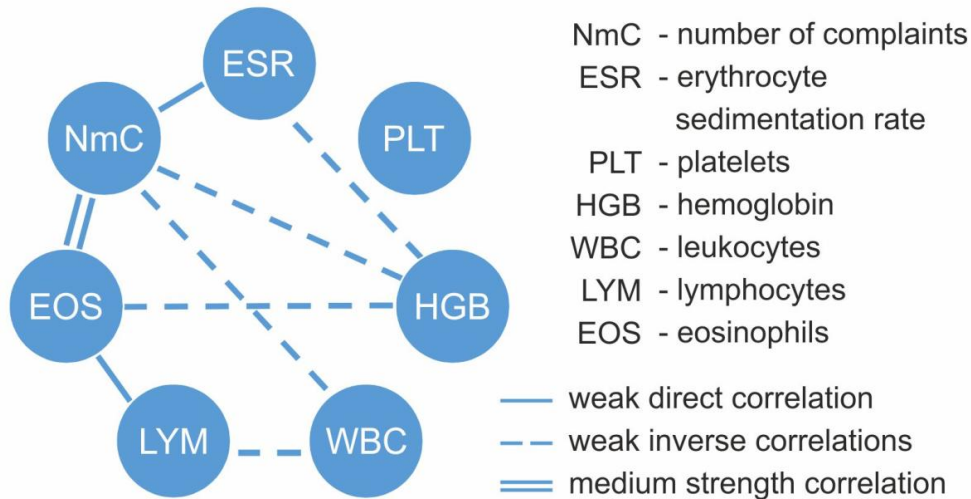


Figure 3. Correlation structure of blood test parameters with the number of TE complaints in HIV-infected patients

The correlation analysis between the number of complaints and blood test parameters (Fig.3) showed a weak direct correlation with ESR ($r = 0.45$), weak inverse correlations with hemoglobin ($r = -0.35$) and leukocyte count ($r = -0.48$), and medium strength direct correlation with eosinophils ($r = 0.53$). Eosinophil counts showed a direct correlation with lymphocyte levels ($r = 0.43$) and an inverse correlation with hemoglobin ($r = -0.37$). Notably, platelet counts were outside the correlation structure, showing no significant ($p < 0.05$) correlations with other parameters. Thus, the correlation analysis data suggest that the higher the severity, activity, and duration of toxoplasmic invasion (as indicated by eosinophilia), the more varied the symptoms (number of complaints), which in turn contributes to increased ESR, leukopenia, and hypochromic anemia

Discussion

Neurological complications are common in patients with HIV infection, even in the era of highly active antiretroviral therapy. TE remains the leading cause of brain lesions in HIV-infected patients.

According to the literature, the prevalence of TE among HIV-infected patients worldwide has variability, depending not only on the state of the immune system but also on socioeconomic, geographic, and medical factors. In some countries in Africa and Latin America, TE prevalence can reach 50-75% among HIV-

positive patients, while in North America, Western Europe, and some regions of Asia, it is as low as 25% [20, 21].

Data from scientific literature and our analysis of CD4+ cell levels in HIV-infected patients with TE demonstrate a strong relationship between the degree of immunosuppression and the risk of developing TE. Many studies indicate that patients with CD4+ cell counts below 100 cells/ μ L have a significantly increased risk of developing TE [12]. However, in our data, TE development was observed even with CD4+ counts below 200 cells/ μ L. This may indicate clinical case-specific factors, genetic, or epidemiological factors that require further study.

When comparing the clinical indicators of our patients with literature data, significant alignment is observed in clinical symptoms. According to our data, general weakness, headache, and fever were the most common symptoms, which coincides with literature data where headache and fever are observed in 50-70% of TE patients [14, 19]. General weakness, a frequent (91.3%) nonspecific symptom in our patients, may be due to both the infection process and the consequences of immune-deficiency. Symptoms such as limb weakness, nausea, unsteady gait, dizziness, speech disturbances, and seizures occurred with moderate frequency in our patients. These results may indicate that the primary manifestations of the

disease are cognitive and psychological disorders, followed by the appearance of local neurological deficits (hemiparesis, speech problems).

As noted in the literature, the presence of IgG antibodies to *T. gondii* is an important but not the only marker of toxoplasmic encephalitis in HIV-infected patients. The absence of IgG does not exclude the diagnosis, especially in patients with severe immunodeficiency.

PCR for *T. gondii* DNA in cerebrospinal fluid can be used to confirm the diagnosis, but its sensitivity is relatively low [18]. A positive result helps confirm TE, but a negative result does not rule out the infection. PCR is often used to exclude other opportunistic infections [20].

MRI data showing typical ring-enhancing lesions with contrast, hyperintensity on T2-weighted images, and surrounding edema play a key role in diagnosis.

If necessary diagnostic tests cannot be performed quickly to clarify the diagnosis, or if anti-toxoplasmosis antibodies are absent, therapy with *trimethoprim/sulfamethoxazole* (Bactrim) *ex juvantibus* may be initiated, as most patients respond to primary therapy [17, 18]. Patients who show no clinical or radiological improvement after 10 days of

therapy should be investigated for other or additional intracranial pathology.

Conclusions

1. TE is a serious complication in HIV-infected patients, observed in those with chronic *T. gondii* infection. Patients with HIV who test positive for *T. gondii* antibodies from the onset of infection should be considered at risk for developing toxoplasmic encephalitis.

2. TE of the brain occurs when CD4 cell counts drop below 200 cells/ μ L and is characterized by multiple symptoms, with an average of 5.67 ± 0.37 symptoms.

3. The most common manifestations of TE were general weakness, headache, fever, nausea, and limb weakness. In the presence of such complaints, even without pronounced focal neurological symptoms, toxoplasmic encephalitis should be suspected.

4. Correlation analysis data suggest that the severity and activity of toxoplasmic invasion (eosinophilia) are directly correlated with the number of complaints, which in turn contributes to increased ESR, leukopenia, and hypochromic anemia.

Conflicts of interest: authors have no conflict of interest to declare.

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КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ТЕЧЕНИЯ ТОКСОПЛАЗМНОГО ЭНЦЕФАЛИТА У ВИЧ ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ

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Резюме. В статье представлены результаты ретроспективного анализа клинических особенностей и результатов обследования у 23 пациентов с токсоплазмозным энцефалитом (ТЕ) у ВИЧ инфицированных больных. Среди обследованных было 11 (47,8%) мужчин и 12 (52,2%) женщин. Возраст пациентов колебался от 31 до 55 лет, в среднем составив $37,5 \pm 0,38$ лет. Среднее количество CD4+ лимфоцитов составляло $102,5 \pm 21,2$ клеток/мкл, а нагрузка РНК ВИЧ в плазме на момент постановки диагноза токсоплазмозного энцефалита (ТЭ) составляла $292773,8 \pm 113180$ копий/мл. У всех пациентов имело место 4-я стадия ВИЧ инфекции (по классификации CDC, 1993). Токсоплазмозная инфекция подтверждалась серологическим анализом крови (ИФА – наличие АТ IgG к токсоплазме), а токсоплазмозный энцефалит – наличием характерных очаговых изменений в головном мозге при МРТ. По результатам нашего анализа токсоплазмозный энцефалит у ВИЧ инфицированных развивается постепенно и первичными проявлениями заболевания являются когнитивные и психические нарушения, затем присоединяются локальные неврологические нарушения (гемипарезы, судороги, проблемы с речью). Всех ВИЧ-Инфицированных пациентов, у которых в начале заболевания выявляются антитела к токсоплазме можно отнести к группе риска развития токсоплазмозного энцефалита. ТЕ выявляется при понижении уровня CD4+ клеток ниже 200 клеток/мкл и характеризуется полисимптомностью, которое в среднем насчитывалось $5,67 \pm 0,37$ симптомов. Данные корреляционного анализа между измененными показателями крови и наличием симптомов при ТЕ у ВИЧ инфицированных, показало, что чем выше степень тяжести, активности и длительности токсоплазмозной инфекции, тем больше наблюдаются разнообразные симптомы.

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