

# Clinical and Laboratory Characteristic of Crypto-Cock Meningitis in HIV-Infected Patients

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**Abstract** One of the most common forms of invasive mycoses in human immunodeficiency virus (HIV) infection is cryptococcal infection. Cryptococcosis is usually subacute meningitis or meningoencephalitis with fever, malaise and headache in HIV-infected patients. The aim of the study was to assess the clinical course of cryptococcal lesions of the central nervous system. The diagnosis was confirmed by isolation of cryptococcus from cerebrospinal fluid by the method of polymerase chain reaction. 10 patients with cryptococcal meningitis were observed. Analysis of the study results revealed the peculiarities of cryptococcosis course in HIV-infected patients.

**Keywords** HIV-infection, Cryptococcus, Meningitis, Clinic, Diagnostics

## 1. Introduction

Invasive mycoses have begun to occupy a special place among all infectious diseases for recent decades. Cryptococcal infection is one of the most common forms. HIV infection is the most important risk factor for this disease. According to the AIDS Clinical Research Unit (New York, USA), cryptococcal meningitis is the most common disease worldwide for people with HIV infection [1]. Studies show that almost 1 million cases of cryptococcal meningitis are diagnosed every year worldwide and a mortality rate makes up over 600,000 [2]. The morbidity has significantly decreased with effective anti-retroviral therapy (ART) and most new cases are found in patients with newly diagnosed HIV infection. [3]. The incidence of cryptococcal infection among people living with HIV (PLHIV) in the United States is low. Among HIV-infected patients with CD4  $\leq$  100 cells /  $\mu$ l, the prevalence of cryptococcal antigenemia was 2.9% and the prevalence was 4.3% among patients with CD4  $\leq$  50 cells /  $\mu$ l [4].

There are no data about cryptococcosis morbidity in Uzbekistan.

Cryptococcosis is usually sub-acute meningitis or meningoencephalitis with fever, malaise and headache in HIV-infected patients. Classical meningeal symptoms and signs occur only from one quarter to one third of patients. Some patients have symptoms of encephalopathy, such as lethargy, altered consciousness, personality changes and memory loss. Cryptococcosis can be diagnosed using a

culture method, cerebrospinal fluid microscopy (CSF) or cryptococcal antigen detection (CrAg). PCR has been increasingly used for diagnostic purposes for recent years and its value is in establishing a diagnosis in the shortest time.

**Aim** of the study was to evaluate the clinical course of cryptococcal lesion of the central nervous system in HIV-infected patients.

## 2. Material and Methods

**Table 1.** The Memorial-Sloan-Kettering scale

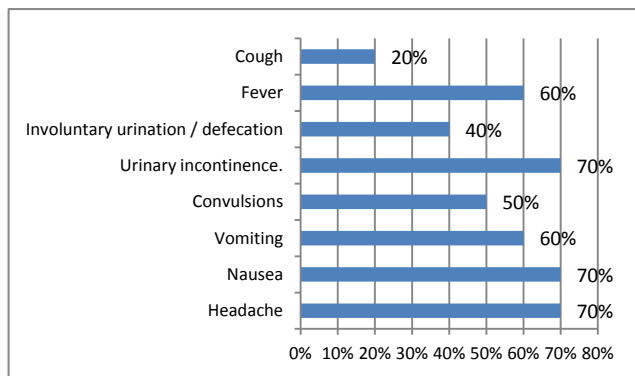
Stage 0:	(norm): Normal cognitive and motor functions
Stage 0.5:	(doubtful / subclinical): Labor and daily activities are not violated. The gait is normal. A mild slowdown in the motility of the eyes and limbs is possible.
Stage 1:	(light): At work and in everyday life can perform any activity except the most difficult one. Unambiguous signs of cognitive or motor disorders. Walking without support is possible.
Stage 2:	(moderate severity): The patient is disabled. In everyday life can perform only simple actions. Gait impairment; may need walking support.
Stage 3:	(severe): Evident cognitive impairment (can no longer absorb meaningful new information, complex conversation is impossible, evident slowdown of psychomotor reactions) or evident motor disorder (walking is possible only with the support of, for example, wheeled walkers, significant slowdown and awkwardness of manual motor skills).
Stage 4:	(final stage): Complete mutism or a condition close to it. Severe spastic tetraparesis or tetraplegia. Urinary and fecal incontinence. Expression and understanding of only the simplest things.

10 patients with cryptococcal meningitis admitted to the Republican Research Centre of Emergency Medicine were observed. Patients were sent to the hospital with primary diagnoses: acute cerebrovascular accident, acute meningoencephalitis, HIV-encephalopathy. In 6 (60%) patients HIV infection was first detected during examination. The remaining patients, knowing about their status, did not undergo examination and did not take ART. The average age of the patients was 39.2 years (19-59). There were 2 (20%) women and 6 (60%) men.

Cerebrospinal fluid, in which cryptococcus was isolated by PCR served as the study material for confirming the diagnosis of cryptococcal meningitis. The severity of the clinical and functional severity of neurocognitive and motor disorders in patients was evaluated by the Memorial-Sloan-Kettering scale (Price 1988) (Tab.1).

### 3. Results and Discussion

At admission, the condition of the patients as severe and extremely severe was detected in 7 (70%) patients who corresponded to stages 3 and 4 by the Memorial-Sloan-Kettering scale. Complete mutism or a state close to it, evident spastic paresis and understanding only the simplest things were observed in 5 (50%) patients.



**Figure 1.** Complaints of patients with cryptococcal meningoencephalitis

At admission, patients or their relatives complained of severe headache, nausea, vomiting, dizziness, unstable gait observed before admission, four patients noted visual disorder (double vision), cough. The severity of the condition was due to evident intoxication and cerebral symptoms.

In 9 (90%) patients meningeal symptoms (stiff neck, Kernig, Brudzinsky symptoms) were revealed, in one patient meningeal symptoms were negative. Convulsions were observed in 5 (50%) patients, dysfunctions of the pelvic organs were revealed in 7 (70%) cases (Fig. 1).

Depletion syndrome was detected in all patients at examination. Diarrhea was detected in 2 (20%) patients; fever for more than 1 month occurred in 6 (60%) patients.

The following opportunistic infections were detected: lymphadenopathy - in 2 (20%) cases, pneumocystic pneumonia - in 1 (10%) patient, oropharyngeal candidiasis - in 5 (50%) cases and tuberculosis - in 1 (10%) observation.

Magnetic resonance imaging (MRI) of the brain was performed in ten patients: diffuse lesions were revealed in 6 (60%) patients and focal changes - in 4 (40%) cases. All patients were performed spinal puncture for diagnostic purposes. A sharp increase in cerebrospinal fluid pressure was revealed, the cerebrospinal fluid was mostly transparent and in 2 cases it was xanthochromic. Cytosis in 4 (40%) patients remained within normal limits, in 6 (60%) patients it was increased from 16 to 200 cells /  $\mu$ l, mainly lymphocytic, protein content was increased (0.66-0.99 g / l) in 6 patients (60%). When performing a general blood test, anemia was detected in 6 (60%) patients, while in 2 cases hemoglobin was 66 and 68 g / l, leukopenia was observed in 3 (30%) patients -  $1.69-3.12 \times 10^9 / l$ , ESR was increased in 9 (90%) patients - 14-75 mm / h. In 4 (40%) patients HIV infection was first detected, 6 (60%) were registered at the AIDS Centers, but did not receive antiretroviral therapy (ART). One of them started ART 4 weeks ago and cryptococcal meningoencephalitis manifested itself as a reconstructive immune reconstitution syndrome. A laboratory examination of immunodeficiency state revealed that all patients were in the stage of deep immunodeficiency: the median of CD-4 lymphocytes was 58.6 (20-69) cells /  $\mu$ l of blood.

Analysis of the study results revealed the peculiarities of cryptococcosis course in HIV-infected patients. The earliest symptoms of the disease were fever, persistent headache, nausea, and vomiting. 90% of patients had meningeal symptoms, although, according to literature, they are found in only 30% of patients suffering from cryptococcosis [5-6]. All patients had a clinical picture of meningoencephalitis, similar to meningoencephalitis of another etiology, subarachnoid hemorrhage and brain tumors which leads to a high incidence of erroneous diagnosis, non-specialized hospitalization and the absence of appropriate treatment. As a result, in 7 (63.6%) patients the disease ended by lethal outcome in the first month of therapy. Mortality reaches 100% in HIV-infected untreated patients at cryptococcal meningoencephalitis. 10–25% of patients die during the initial period of therapy, another 30–60% die within the next 12 months [7-8].

In this regard, there is an urgent need for early diagnostics and intensive care of cryptococcosis. However, the clinical signs of infection are often nonspecific, and laboratory confirmation is difficult. Prospective controlled trials show that prophylactic fluconazole or itraconazole can reduce the incidence of primary cryptococcal disease in patients with CD4 <100 cells /  $\mu$ L [9-10]. In Uzbekistan, according to Appendix No. 4 to the order of the Ministry of Health of the Republic of Uzbekistan dated by March 04, 2015 No. 81 “NATIONAL CLINICAL PROTOCOL. TREATMENT MANAGEMENT OF PATIENTS WITH OPPORTUNISTIC INFECTIONS AND GENERAL SYMPTOMS OF HIV / AIDS” Cryptococcus neoformans for PLHIV with a CD4  $\leq$  50 cells /  $\mu$ l was prevented with Fluconazole 100 mg once a day. In the order of the Ministry of Health of the Republic of Uzbekistan dated by April 30, 2018 No. 277 “On the implementation of national clinical

protocols on HIV infection”, the primary prevention of cryptococcal infection must be started with a CD4 level of  $\leq 100$  cells /  $\mu\text{l}$ .

#### 4. Conclusions

Cryptococcal meningitis in HIV-infected patients is observed at evident immunodeficiency (a decrease in CD-4 lymphocytes of less than 100 cells /  $\mu\text{l}$ ) and is characterized by a severe progressive course with high mortality in the first month of therapy. In 40 (40%) patients HIV infection was first detected at the time of the examination - CNS lesion by cryptococcosis was the primary manifestation of HIV. Modern diagnostics of CNS lesions in HIV should include a study on cryptococcosis of patients with CD-4 lymphocytes of less than 100 cells /  $\mu\text{l}$ .

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