

CEREBROSPINAL FLUID PROFILES IN ACQUIRED IMMUNODEFICIENCY SYNDROME WITH AND WITHOUT NEUROCRYPTOCOCCOSIS

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SUMMARY

Cryptococcosis is one of the most common fungal infections of the central nervous system (CNS) in AIDS patients and meningoencephalitis or meningitis is a frequently observed manifestation. However, systematic studies of cerebrospinal fluid (CSF) composition from AIDS patients with CNS cryptococcosis have been few. CSF samples from 114 HIV seropositive patients whose clinical complaint suggested CNS involvement, were analyzed; 32 samples from patients diagnosed as having neurocryptococcosis (Group 1) and 82 samples from patients with no identified neurological dysfunction (Group 2). Based on cytological and biochemical results, two distinct profiles were observed: Normal (Group 1 = 31%, Group 2 = 39%); Abnormal (Group 1 = 69%, Group 2 = 61%). Lymphocytes were the most frequent cells in both groups. Our CSF cytological and biochemical findings showed that in AIDS patients liquoric abnormalities are quite frequent, non-specific and difficult to interpret. In these circumstances a systematic search to identify the etiologic agent using microbiological and/or immunological assays must be routinely performed.

KEYWORDS: AIDS; Cerebrospinal fluid; *Cryptococcus neoformans*; Neurocryptococcosis.

INTRODUCTION

Patients with acquired immunodeficiency syndrome (AIDS) are frequently affected by neurological disorders. Some of these are due to opportunistic infections but others, such as progressive dementia, appear to result from direct brain involvement by the human immunodeficiency virus (HIV)¹. Central nervous system (CNS) infection by HIV can occur early in the patient's illness with no evidence of neurological abnormalities being detected during a clinical examination¹. Although a neurological history and clinical examination are important in the diagnosis of both primary and secondary processes, additional diagnostic tests are frequently utilized. One of the most common procedures is cerebrospinal fluid (CSF) analysis. However, the interpretation of CSF findings in HIV-infected patients may be difficult due the diversity of alterations that this virus can produce in CSF composition, even in the absence of secondary complications. Thus, for example, the CSF inflammatory response may be absent or altered either by the virus itself or by other pathogens, as in the case of patients with HIV-cryptococcal meningitis².

Cryptococcosis is one of the most common fungal infections of the CNS and the second most important opportunistic disease observed in AIDS patients⁹. Although dissemination of the disease may affect virtually any organ, meningoencephalitis or meningitis is the manifestation most frequently observed³. To date, however, systematic studies of CSF composition from AIDS patients with CNS cryptococcosis have been few.

The present study examined the frequency of liquoric alterations and the cytological and biochemical profiles of CSF samples from HIV-infected patients with neurocryptococcosis and in those with no identified neurologic disorder.

MATERIAL AND METHODS

Cerebrospinal fluid samples from 114 HIV seropositive patients attended at the University Hospital of the State University of Campinas (Campinas, São Paulo, Brazil) were analyzed in the present study. All these patients were submitted to lumbar puncture based on their clinical complaint suggesting

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CNS involvement. For this reason the phase of the HIV infection was not considered. All the samples underwent a standard laboratory screening which included manual global and differential cell counts (using a Fuchs-Rosenthal chamber and cytocentrifuged, air-dried hematological smears stained by the May-Grunwaldt method), neoplastic cytology, glucose determination (by the glucose-oxidase reaction), total protein quantification (trichloroacetic acid turbidimetric method), bacterioscopy and/or direct examination and culture for common aerobic pathogens, yeasts and mycobacteria, in addition to serological tests for antibody detection in toxoplasmosis, syphilis and neurocysticercosis and antigen detection in cryptococcosis. The neoplastic cytology, the serological tests for antibody detection, the bacterioscopy and culture for common aerobic pathogens and mycobacteria were negative in all CSF samples. Thirty-two of 114 patients were diagnosed as having neurocryptococcosis based on direct examination (China ink preparation), culture for yeasts and detection of specific antigens from *C. neoformans*, using a cryptococcal antigen latex agglutination system (Meridian Diagnostics, Inc., OH, USA). Based on the above laboratory data, the patients were classified either as Group I (patients with neurocryptococcosis, n = 32) or Group II (patients with no identified neurological pathology, n = 82).

RESULTS

The cytological and biochemical results from HIV patients, 32 with neurocryptococcosis (Group 1) and 82 with no identified neurological pathology (Group 2) are shown in the Table 1. Essentially two CSF profiles were observed: Profile I: defined as normal CSF (white blood cells, $WBC \leq 3/mm^3$, total protein ≤ 44.0 mg/dl and glucose ≥ 40.0 mg/dl). Thirty-one percent of the patients from Group 1 and 39% of those from Group 2 fulfilled these criteria; Profile II: defined as abnormal CSF ($WBC \geq 4/mm^3$, and/or total protein ≥ 45 mg/dl, and/or glucose ≤ 30 mg/dl). This profile was found in 69% of the patients from Group 1 and in 61% of the patients from Group 2.

The differential counts showed a predominance of lymphocytes in 89% of the patients from Group 1 and in 80% of those from Group 2.

DISCUSSION

HIV is neurotropic and may be cultured from the CSF of infected individuals, regardless of the presence or absence of neurological abnormalities, i.e. a positive CSF culture may not explain a particular clinical problem. This does not occur in other viral infections of the CNS, in which a positive culture represents definitive evidence of the etiology. Similarly, a negative culture does not exclude HIV as the etiologic agent of the neurological abnormalities⁶.

CNS disorders may occur at all stages of the HIV infection^{6,10}. McARTHUR et al.¹¹ demonstrate a high rate of CSF abnormalities independent of neuropsychiatric findings or time since infection. The abnormalities noted on neurological testing were, in most cases, subtle and do not necessarily presage progressive disease.

The CSF of immunocompetent patients with neurocryptococcosis usually shows an elevated opening pressure, a mild hypercytosis with the presence of lymphocytes, monocytes, neutrophils and sometimes eosinophils, a slight increase in total protein content and a decrease in glucose concentration. A mycological examination frequently shows the presence of a yeast upon direct examination in a cell counting chamber, in China ink preparations or on stained slides after cytocentrifugation. High titers of antigen can be detected by latex agglutination⁹.

In AIDS patients with neurocryptococcosis, the CSF composition may differ from the classical profile described above. The absence of an inflammatory response in patients with HIV-related cryptococcal meningitis has been described by several authors^{3,4,7,8,9,13}. The present study has shown that 31% of the patients with cryptococcosis had a normal CSF based on the cytological and biochemical parameters chosen. This finding is similar to that reported by LIVRAMENTO et al.⁹, although REIS-FILHO et al.¹⁴ found a lower frequency (21.7%) in their patients.

TABLE 1
Comparison of the cytological and biochemical profiles of CSF samples from the two groups of HIV — infected patients.

CSF Analysis	Group 1 (n = 32)		Group 2 (n = 82)	
	Profile I (n = 10)	Profile II (n = 22)	Profile I (n = 32)	Profile II (n = 50)
Leucocytes/mm ³	1.1 (0-2)	18.3 (0-94)	1.1 (0-3)	21.6 (0-324)
Lymphocytes (%)	—	85.4 (4-100)	—	79.4 (0-100)
Neutrophils (%)	—	12.6 (0-96)	—	17.1 (0-97)
Protein (mg/dl)	27 (14-37)	63.1 (23-194)	28 (6-44)	66.6 (17-195)
Glucose (mg/dl)	67 (42-106)	39.6 (0-66)	56 (43-98)	50.4 (12-115)

Group 1: Patients with neurocryptococcosis; **Group 2:** Patients with no identified neurological disorder. **Profile I:** normal CSF; **Profile II:** abnormal CSF. All results are expressed as the mean with the range shown in parenthesis.

Our observations agree with those of other authors^{2, 9, 14} who also found a minimum inflammatory response, a predominance of lymphocytes, a normal glucose level and a slight increase in total protein in the CSF samples of similar patients. It is interesting to note that 61% of the patients without CNS involvement showed some degree of liquoric alteration (Profile II). APPLEMAN et al.¹, examining CSF from 114 HIV asymptomatic infected individuals, found that almost 40% of CSF samples examined, had at least one abnormality. In the other hand, some alterations such as mild protein elevation and low-grade lymphocytic pleocytosis, were seen with equal frequency in the same population studied. Several other authors have also found CSF abnormalities in HIV seropositive patients with no CNS involvement^{5, 6, 10, 12}. Since abnormal CSF responses in HIV seropositive patients may mimic alterations caused by infectious or neoplastic processes, there may be difficulty in providing a correct diagnosis. Our cytological and biochemical findings for CSF confirmed previous observations that in AIDS patients liquoric abnormalities are quite frequent, non-specific and difficult to interpret. In these circumstances, a systematic and routine search for the etiologic agent is of great importance. With regard to cryptococcosis, specific tests using China ink preparations to look for the presence of a yeast and the latex agglutination reaction to detect cryptococcal antigen must be routinely performed.

RESUMO

Perfis liquóricos na síndrome da imunodeficiência adquirida com e sem neurocriptococose

A criptococose é uma das infecções fúngicas mais comuns do sistema nervoso central (SNC) em pacientes com Síndrome da Imunodeficiência Adquirida (SIDA), sendo meningoencefalite ou meningite manifestações frequentemente observadas. Apesar disso, poucos são os estudos sistemáticos sobre a composição do líquido céfalo-raquidiano (LCR) de pacientes com SIDA e neurocriptococose. No presente estudo, foram analisadas amostras de LCR de 114 pacientes soropositivos para HIV, com queixa clínica sugestiva de envolvimento do SNC, sendo 32 com neurocriptococose (Grupo 1) e 82 sem doença neurológica identificada (Grupo 2). Considerando os resultados citológicos e bioquímicos, dois perfis liquóricos foram observados: Normal (Grupo 1 = 31%, Grupo 2 = 39%) e Anormal (Grupo 1 = 69%, Grupo 2 = 61%). Linfócitos foram as células predominantes em ambos os grupos. Nossos resultados mostram que, entre os pacientes com SIDA, anormalidades liquóricas são bastante frequentes, inespecíficas e difíceis de serem interpretadas. Assim, entendemos que nessas condições, a análise do LCR

deve, necessariamente, ser complementada pela busca sistemática do agente etiológico através de métodos microbiológicos e/ou imunológicos.

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