



ORIGINAL ARTICLE

Characterization of patients with Human Immunodeficiency Virus positive for meningeal cryptococcosis diagnosed by cerebrospinal fluid study at Regional Teaching Hospital of Ambato

Caracterización de pacientes con Virus de Inmunodeficiencia Humana positivos a criptococosis meníngea diagnosticados por estudio de líquido cefalorraquídeo en el Hospital Regional Docente De Ambato

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ABSTRACT

Introduction: Human Immunodeficiency Virus is a global health problem, which leads to the development of opportunistic infections in patients.

Objective: to characterize patients with Human Immunodeficiency Virus positive for meningeal cryptococcosis.

Methods: observational, descriptive, cross-sectional study in patients with Human Immunodeficiency Virus positive to meningeal cryptococcosis diagnosed by cerebrospinal fluid study in the Regional Teaching Hospital of Ambato in the period 2018-2021. The sample (n=155) was selected by simple random sampling.

Results: male sex (78,7 %) and ages between 31 and 40 years (36,1 %) predominated; the main symptomatology was headache (69 %), fever (42,6 %) and nausea (31 %). 22,6 % of the patients were not adherent to antiretrovirals, 23,2 % had CD4 count < 500/mm³ and 43,9 % were drug users. Of the patients, 51,6 % had values higher than 100 mg/ dL protein, 51 % had values lower than 29 mg/ dL glucose in cerebrospinal fluid. Protein alterations were associated with CD4 levels (p<0.01) and viral load (p<0,05).

Conclusions: patients with Human Immunodeficiency Virus of male sex, aged between the third and fourth decade of life, who do not adhere to antiretroviral therapy and/or consume drugs are prone to the development of meningeal cryptococcosis. Cytochemical analysis of cerebrospinal fluid is useful as a biomarker of unfavorable prognosis in patients with meningeal cryptococcosis.

Keywords: VIH; Cryptococcosis; Cerebrospinal Fluid; Opportunistic Infections; Biomarkers.

RESUMEN

Introducción: el Virus de Inmunodeficiencia Humana constituye un problema de salud a escala global, que propicia en los pacientes el desarrollo de infecciones oportunistas.

Objetivo: caracterizar a los pacientes con Virus de Inmunodeficiencia Humana positivos a criptococosis meníngea.

Métodos: estudio observacional, descriptivo, transversal en pacientes con el Virus de Inmunodeficiencia Humana positivos a criptococosis meníngea diagnosticado por estudio de líquido cefalorraquídeo en el Hospital Regional Docente de Ambato en el periodo 2018-2021. La muestra (n=155) se seleccionó por un muestreo aleatorio simple.

Resultados: predominó el sexo masculino (78,7 %) y las edades entre 31 y 40 años (36,1 %); la principal sintomatología fue la cefalea (69 %), fiebre (42,6 %) y náuseas (31 %). El 22,6 % de los pacientes no se adhería a los antirretrovirales, el 23,2 % presentó conteo de CD4 < 500/mm³ y el 43,9 % consumía drogas. El 51,6 % de los pacientes presentaron valores superiores a 100 mg/ dL proteínas, el 51 % inferiores a los 29 mg/ dL de glucosa en líquido cefalorraquídeo. Las alteraciones de las proteínas mostraron asociación con los niveles de CD4 (p<0,01) y la carga viral (p<0,05).

Conclusiones: los pacientes con Virus de Inmunodeficiencia Humana del sexo masculino, en edades entre la tercera y cuarta década de vida, que no se adhieren a la terapia antirretroviral y/o consumen drogas son propensos al desarrollo de criptococosis meníngea. El análisis citoquímico del líquido cefalorraquídeo resulta útil como biomarcador de pronósticos desfavorables en pacientes con criptococosis meníngea.

Palabras clave: VIH; Criptococosis; Líquido Cefalorraquídeo; Infecciones Oportunistas; Biomarcadores.

INTRODUCTION

Human immunodeficiency virus (HIV) is currently a global public health problem.⁽¹⁾ Thanks to prevention campaigns and the introduction of antiretroviral therapies, the number of cases in industrialized countries has decreased.⁽²⁾ However, in developing countries, the prevalence of opportunistic diseases, including fungal or fungal etiologies such as cryptococcosis remains high, due to low patient adherence to antiretroviral therapy, limited access to medical care, poverty and lack of knowledge of the HIV-positive person, making them more susceptible to various diseases.

Cryptococcus neoformans is an important opportunistic pathogen involved in the death of high percentages of HIV/AIDS patients in most developing countries.⁽³⁾ This opportunistic mycosis affects the brain as well as the meningeal, pulmonary and systemic levels.⁽⁴⁾ Cryptococcal meningitis is one of the main factors in early mortality and accounts for up to 20 % of all deaths.⁽⁵⁾

A total of 223 100 cases of meningeal cryptococcosis were estimated to have occurred worldwide in people living with HIV, with the third largest number of cases worldwide coming from Latin America, with an estimated incidence of 5,300 cases per year. Of these, Brazil and Colombia were the countries with the highest incidence, between 1001 to 2500 cases, followed by Argentina and Mexico with an incidence of 501 to 1000 cases.⁽⁶⁾

In Ecuador, the cities of Quito and Guayaquil have reported prevalences of 8 % and 33 %, respectively, in adults over 18 years of age and hospitalizations. Given the paucity of sources and the importance of published data, there is reason to believe that this disease is under-reported or under-reported.⁽⁷⁾

According to investigators' estimates, Phase 2 clinical trials in cryptococcal meningitis, early antifungal activity (EFA) of *Cryptococcus* isolated from cerebrospinal fluid (CSF) is used as an alternative endpoint for all-cause mortality.⁽⁸⁾

In their study focused on measuring cerebrospinal fluid lactate levels as a prognostic marker, the authors were able to conclude that, baseline CSF lactate levels at the point of care are a prognostic marker of disease severity and mortality in cryptococcal meningitis. Individuals with an elevated baseline CSF lactate level are more likely to have altered mental status, seizures, and elevated CSF opening pressure with an increased risk of death.⁽⁹⁾

The investigators of the present study highlight the lack of studies on meningeal cryptococcosis in HIV patients in Ecuador, especially at the regional level. Therefore, the present investigation was developed with the objective of characterizing patients with Human Immunodeficiency Virus positive for meningeal cryptococcosis diagnosed by cerebrospinal fluid study at the Hospital Regional Docente de Ambato.

METHODS

A descriptive, observational and cross-sectional research was conducted in patients with HIV positive to Meningeal Cryptococcosis by CSF study at the Hospital Regional Docente de Ambato in the period 2018-2021.

The universe was composed of a total of 257 patients. The sample (n=155) was established by simple random sampling by calculating for finite population, using the following formula:

$$n = \frac{N \times Z_a^2 \times p \times q}{d^2 \times (N - 1) + Z_a^2 \times p \times q}$$

Where:

N = population size (257).

Z = confidence level (1,960).

P = probability of success, or expected proportion (95 %).

Q = probability of failure (5%).

D = precision (maximum admissible error in terms of proportion) (3 %).

All HIV-positive patients diagnosed with cryptococcosis by CSF study, attended at the Regional Teaching Hospital of Ambato, and who were older than 18 years were included. Those with incomplete data in individual clinical history, those referred to another health center or with concomitant entities were excluded.

The hospital database and medical records were used for data collection. A data collection form was prepared for data collection.

The data were organized using the Microsoft Excel program and later analyzed using the SPSS program. Descriptive statistics were used for data analysis, using absolute and relative percentage frequencies.

RESULTS

There was a predominance of male patients (78,7 %) and the age group 31 to 40 years (36,1 %) (Table 1).

Table 1. Sociodemographic characteristics of patients with HIV-positive meningeal cryptococcosis.

Variables		No.	%
Gender	Female	33	21,3
	Male	122	78,7
Age	17 to 25 años	21	13,5
	26 to 30 años	30	19,4
	31 to 40 años	56	36,1
	41 to 50 años	28	18,1
	>50 years old	20	12,9
	Total	155	100

Regarding the symptoms related to meningeal cryptococcosis, 69 % reported experiencing headache, 42,6 % fever and 31 % nausea (Table 2).

Table 2. Clinical symptoms of patients with HIV-positive meningeal cryptococcosis.

Symptom	No.	%
Headache	107	69
Nausea	48	31
Vomiting	38	24,5
Fever	66	42,6
Seizures	47	30,3
Weight loss	20	12,9
Adenopathy	9	5,8
Loss of consciousness	7	4,5
Diplopia	41	26,5
Photophobia	4	2,6
Tinnitus	15	9,7
Confusion	4	2,6
Neck stiffness	5	3,2
Gait disturbance	30	19,4

It was identified that 22,6 % of the patients did not adhere to ARV treatment, 23.,2 % presented a CD4 count < 500/mm³ and 43,9 % consumed drugs (Table 3).

Table 3. Risk factors for the development of meningeal cryptococcosis in HIV-positive patients.

Variables		No.	%
Taking ARVs	yes	120	77,4
	No	35	22,6
CD4	500/mm ³	119	76,8
	200 - 499/mm ³	23	14,8
	< 200/mm ³	13	8,4
Viral load	0 - 5000	116	74,8
	5001 - 19000	27	17,4
	19001 - 54000	10	6,5
	>54000	2	1,3
Drug addiction	yes	68	43,9
	No	87	56,1

Altered values were observed in proteins, where 51,6 % of the patients presented values higher than 100 mg/ dL (proteinorrachia). On the other hand, glucose levels showed predominance of glucorrachia (low glucose values), where 51 % presented values lower than 29 mg/ dL. With regard to the India ink staining, 91 % were tested in order to facilitate the detection of cryptococcus neoformans and minimize the risk of meningitis.

Table 4. Diagnostic method, direct examination and culture of cerebrospinal fluid.

Variables		No.	%
Proteins mg/ dL	< 60 mg/ dL	7	4,5
	60 a 83 mg/dL -Normal	47	30,3
	84 a 100 mg/dL	21	13,5
	>100 mg/dL	80	51,6
Glucose mg/ dL	< 29 mg/ dL	79	51,0
	30 a 35 mg/ dL	21	13,5
	36 a 45 mg/ dL	37	23,9
	46 a 49 mg/dL	3	1,9
	50- 70 mg/dL	15	9,7
India ink staining	Si	141	91,0
	No	14	9,0

The efficacy of CSF study as a biomarker of disease progression was studied. Table 5 shows the relationship of the markers (Proteins, Glucose and India ink staining), with CD4 values and viral load. Only protein alterations showed association with CD4 levels ($p < 0.01$) and viral load ($p < 0.05$).

Table 5. Efficacy of the CSF method as a biomarker of disease progression.

		CD4	Viral Load
Proteins mg/dL	Pearson correlation	0,210**	0,203*
	Sig. (bilateral)	0,009	0,011
Glucose mg/dL	Pearson correlation	-0,111	-0,144
	Sig. (bilateral)	0,170	0,074
Chinese ink staining	Pearson correlation	-0,015	0,007
	Sig. (bilateral)	0,849	0,928

*The correlation is significant at the 0.05 level (bilateral).

**Correlation is significant at the 0.01 level (bilateral).

DISCUSSION

Cryptococcosis is an invasive mycosis caused mainly by *Cryptococcus neoformans*. This disease mainly affects immunocompromised patients, especially those with HIV infection, with the male gender being the most affected in the population.

One study identified that 78,8 % of the patients were male with a median age of $40,1 \pm 11,9$ years. The 72,7 % had HIV disease, 20 % were immunocompetent and 9,1 % had pharmacological immunosuppression mainly due to autoimmune pathologies.⁽¹⁰⁾ Similarly, other studies have reported a predominance of males, which coincides with the present study.⁽¹¹⁾

HIV research has shown that men have a higher risk of developing cryptococcosis than women. This fact may be influenced by the fact that, to a greater extent, patients living with HIV are male, which has been reported in numerous studies.^(12,13)

The study by Ancona-Castro et al.⁽¹⁴⁾ found results very similar to the study, the symptoms and signs reported were confusion and altered mental status in seven cases (100 %), headache in five cases (71,4 %), nausea and vomiting in five cases (71,4 %), fever in five cases (71.4 %) and meningeal signs in 4 cases (57,1 %). On the other hand, the study by Aveiro et al.⁽¹⁵⁾ identified that 91 % of the symptoms on admission were neurological, with headaches predominating. Similar results were reported in the present study.

Aveiro et al.⁽¹⁵⁾ identified that the absence of ARV represents one of the risk factors for the development of opportunistic infections in HIV patients. In their study, 100 % of the patients had no antiretroviral treatment at admission, 74 % were unaware that they were HIV-infected and 26 % were not on treatment. The mean viral load was 867,464 copies/ml, the median CD4 cell count was 34 cells/mm³ and 100 % < 150 cells/mm³.

Non-adherence to therapy may be determined by several factors, such as lack of knowledge of the disease, poor medical coverage, socio-educational level of the individual, as well as the presence of adverse drug effects. It is known that drugs can have multiple adverse effects, including hematological disorders.

Hematological alterations are associated with the toxicity of antiretroviral drugs and the clinical conditions of the HIV-positive patient, resulting in altered hematopoiesis affecting all three cell lines, patients may present anemia, leukopenia, thrombocytopenia and/or pancytopenia.⁽¹⁶⁾

With regard to diagnostic methods, Aveiro et al.⁽¹⁵⁾ identified glycorrachia (37 mg/dl), proteinorrachia (174 mg/dl), cellularity \leq 6 cells/ μ l (46 %), 98 % with mononuclear predominance, results that resemble the present ones.

CONCLUSIONS

Patients with Human Immunodeficiency Virus of the male sex, aged between the third and fourth decade of life, who do not adhere to antiretroviral therapy and/or consume drugs are prone to the development of meningeal cryptococcosis. Cytochemical analysis of cerebrospinal fluid is useful as a biomarker of unfavorable prognosis in patients with meningeal cryptococcosis.

Conflicts of Interest

The authors declare no conflicts of interest in relation to the present investigation.

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The authors declare that they have not received funding for the development of this research.

Statement of Authorship

All authors participated in conceptualization, research, writing - initial draft, writing - revision and editing.

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