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Original article

# Cryptococcosis in an Infectious Diseases Hospital of Buenos Aires, Argentina. Revision of 2041 cases: Diagnosis, clinical features and therapeutics

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### ABSTRACT

**Background:** Cryptococcosis is still a life-threatening mycosis that continues to be of serious concern in Latin American countries, especially among HIV+positive population. However, there is not any reliable information about the prevalence of this disease in this region.

**Aims:** The aim of this study is to report data of 2041 patients with cryptococcosis that were attended at the Infectious Diseases Hospital F. J. Muñiz over a 30 year-period.

**Methods:** Information about demographic and clinical data, survival time and the applied treatment, was taken from the Mycology Unit database. Mycological exams from different clinical samples were performed. Cryptococcal capsular antigen in serum and cerebrospinal fluid was detected through the latex agglutination technique. *Cryptococcus* isolates were phenotypically identified and the genotype was determined in some of them. Susceptibility tests were carried out following M27-A3 document.

**Results:** Seventy five percent of HIV+positive patients and 50% of the HIV-negative population were males. Mean ages were 34.1 in HIV+positive patients and 44.8 in the HIV-negative. Cryptococcosis was associated with AIDS in 98% of the cases. Meningeal compromise was seen in 90% of the patients. Although cerebrospinal fluid rendered more positive results, blood culture was the first diagnostic finding in some cases. Cryptococcal antigen showed positive results in 96.2% of the sera samples and in the 93.1% of the cerebrospinal fluid samples. Most of the isolates were *Cryptococcus neoformans* and belonged to genotype VNI. Minimal inhibitory concentration values were mostly below the epidemiological cutoff values.

**Conclusions:** We observed that thanks to a high level of clinical suspicion, early diagnosis, combined therapy and intracranial pressure control by daily lumbar punctures, the global mortality rate has markedly decreased through the years in the analyzed period.

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## Criptococosis en un hospital de enfermedades infecciosas de Buenos Aires, Argentina. Revisión de 2.041 casos: aspectos diagnósticos, clínicos y terapéuticos

### RESUMEN

**Antecedentes:** La criptococosis es una micosis grave y un motivo de preocupación en América Latina, en especial en los pacientes positivos para el VIH. Sin embargo, no existen aún datos regionales fiables acerca de la prevalencia de la enfermedad.

**Objetivos:** Presentar los datos de 2.041 pacientes con criptococosis atendidos en la Unidad de Micología del Hospital de Infecciosas F. J. Muñiz de Buenos Aires, recogidos en un período de 30 años.

*Palabras clave:*

Criptococosis

Diagnóstico de la criptococosis

Micosis asociadas con el sida

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**Métodos:** Se presentan datos demográficos, diagnósticos, clínicos y el tiempo de supervivencia de los pacientes, obtenidos de la base de datos de la Unidad de Micología. Se realizaron exámenes micológicos de diversas muestras clínicas, además de antigenemia y antigenorraquia por aglutinación de látex para *Cryptococcus* en el momento del diagnóstico y durante el seguimiento. Se llevó a cabo la identificación fenotípica de los aislamientos y en numerosos casos también se efectuó la genotipificación. La determinación de los valores de concentración mínima inhibitoria frente a diversos antifúngicos se realizó según el documento M27-A3 (CLSI).

**Resultados:** El 75% de los pacientes positivos para el VIH y el 50% de los no portadores eran varones; la media de edad fue 34,1 años para los positivos para el VIH y 44,8 para los no portadores. La criptococosis se asoció con el sida en el 98% de los casos y el 90% de ellos presentó compromiso meníngeo. Aunque la muestra clínica con mayor porcentaje de resultados positivos fue el LCR, en numerosas ocasiones el hemocultivo fue el primer elemento diagnóstico. La antigenemia fue positiva en el 96,2% de los casos y la antigenorraquia en el 93,1%. La mayor parte de las cepas era *Cryptococcus neoformans* y pertenecía al genotipo VNI, y la concentración mínima inhibitoria en las pruebas de sensibilidad a los antifúngicos de la mayoría de ellos mostró valores inferiores al punto de corte epidemiológico.

**Conclusiones:** Observamos que un alto nivel de sospecha clínica, el diagnóstico temprano, el tratamiento combinado y el control de la presión intracraneal mediante punciones lumbares diarias han permitido disminuir la mortalidad global a lo largo de los años en el período analizado.

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From the onset of the AIDS' pandemic, cryptococcosis has been one of the opportunistic infections associated with this condition, being the third most frequent mycoses after oropharyngeal candidiasis and pulmonary pneumocystosis.<sup>54</sup> Cryptococcosis annual incidence in industrialized countries reaches 2–3% and goes higher in developing countries such as Argentina, where it is about 8–10% in HIV-positive patients requiring hospitalization. Approximately one million new cases of cryptococcal meningitis are registered annually and 650,000 of them die as a result of this mycosis.<sup>60</sup> Although these figures seem to have decreased slightly,<sup>63</sup> in Latin American countries the amount of cases continues to be of serious concern. There is not available information about the global prevalence of this disease in the region, and there is only isolated data from the national surveillance in some countries like Colombia.<sup>30,31</sup>

The first case of cryptococcosis associated with AIDS at the Infectious Diseases Hospital F. J. Muñoz was diagnosed in 1983. In the nineties of the last century approximately 3 new cases per week were attended, and in the last 5 years 60 new patients on average have been diagnosed yearly in this institution. At the present time, it is still the most frequent systemic mycosis in HIV-infected patients in the former hospital followed by pneumocystosis and histoplasmosis.

As cryptococcosis notification is not mandatory in Argentina there is not available information about its incidence and prevalence. According to unpublished statistical data of Buenos Aires Mycology Net, near 50% of AIDS related cryptococcosis diagnosed and treated in Buenos Aires City belong to F. J. Muñoz Hospital. The aim of this study is to show the Mycology Unit experience in the diagnosis of cryptococcosis, and clinical features, therapeutics and progress of patients attended at the F. J. Muñoz Hospital in the last 30 years.

## Materials and methods

### Patients

Mycology Unit database was used to obtain the information about cryptococcosis in patients diagnosed or attended at the F. J. Muñoz Hospital between January 1986 and December 2015. When available, a retrospective analysis of the demographic data, such as underlying conditions, lesion localization, clinical and images features, CD<sub>4+</sub> counts, clinical samples used for diagnosis, cryptococcal polysaccharide capsular antigen titers (in serum and cerebrospinal

fluid – CSF), molecular identification of the isolates and their antifungal susceptibility, treatment schemes and survival time, was carried out.

### Diagnostic methods

Direct examination and cultures were made on the following clinical samples: CSF, blood, muco-cutaneous scrapings, urine, skin and other organ biopsies, lymph node and bone marrow aspirations, bronchoalveolar lavages, sputa or other bronchial secretions, peritoneal and pleural fluids, and other clinical samples (Table 3). All the samples were processed according to the standard methodology of the Mycology Unit.<sup>5,8–10,37</sup> Alcian blue or mucicarmin stains were used in histopathological preparations.<sup>17,22</sup>

Phenotypical differentiation between *Cryptococcus neoformans* and *Cryptococcus gattii* was carried out by seeding on glycine-canavanin-bromothimol blue agar (GCB) and glycine-cycloheximide-phenol red agar (Salkin medium).<sup>43,65</sup> Molecular identification through PCR-RFLP of URA5 gen was carried out in some of the isolates. PCR products were subjected to a double enzymatic digestion with *Sau96I* and *HhaI*, and restriction fragments were separated by electrophoresis in agarose gel and compared with the patterns obtained from the following reference strains: *C. neoformans* var. *grubii*: CBS 10085 VNI, CBS 10084 VNII; *C. neoformans* hybrid AD: CBS 10080 VNIII; *C. neoformans* var. *neoformans*: CBS 10079 VNIV; and *C. gattii*: CBS 10078 VGI, CBS 10082 VGII, CBS 10081 VGIII, and CBS 10101 VGIV.<sup>16,51,52</sup>

Presence and titer of capsular polysaccharide antigen (CrAg) in serum and CSF were determined by the latex agglutination technique (LA) (IMMY, Immunomycologics, Norman Kew Surrey, OK, USA) at diagnosis and during the follow up. Lateral flow chromatography (LFC) (IMMY, Immunomycologics) was just used in the last three years (209 samples) in patients with a clinical suspicion of the disease; whenever the test was positive, the titer was determined by LA, and CSF and other samples were taken to confirm the cryptococcosis. In order to determine the CrAg titer in HIV patients the following serum and CSF dilutions were used: 1:10, 1:100, 1:1000, 1:5000 and 1:10,000. In the case of HIV-negative patients the standard dilutions (1:2<sup>n</sup>) were tested.<sup>5</sup>

Minimal inhibitory concentration (MIC) by means of the broth microdilution technique according to M27-A3 and M27S4 documents of the Clinical Laboratory Standard Institute – USA, were assessed to study the antifungal susceptibility of *Cryptococcus*

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