



## ***Cryptococcus gattii* meningoencephalitis in a pediatric patient with cirrhosis: A case report**

Meningoencefalitis por *Cryptococcus gattii* en un paciente pediátrico con cirrosis: Reporte de caso

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### Resumen

**Introducción:** En Colombia, la criptococosis es una infección fúngica invasiva poco frecuente. **Objetivo:** Reportar el caso clínico de un niño con meningoencefalitis por *Cryptococcus gattii* que tenía como factor de riesgo una disfunción inmune asociada a cirrosis, un factor de riesgo descrito en adultos, pero no reportado en niños. **Materiales y métodos:** Se realizó una revisión no sistemática de la literatura y un resumen de los aspectos más relevantes de la historia clínica. **Resultados:** Se presenta el caso de un paciente masculino de 16 años con antecedente de cirrosis quien consultó por un cuadro clínico de 8 días de evolución de fiebre, emesis persistente, cefalea frontal, fotofobia y tinitus. Al examen físico no presentaba alteraciones neurológicas. En el estudio del líquido cefalorraquídeo las pruebas moleculares directas fueron positivas para *Cryptococcus neoformans/gattii* y el cultivo reportó crecimiento de *Cryptococcus gattii*. **Conclusiones:** En este caso se destaca la importancia de sospechar infecciones oportunistas en pacientes que tienen inmunodeficiencia no solo secundaria a las infecciones por VIH, sino también a la producida por otros factores que alteran la respuesta inmunológica como la cirrosis.

**Palabras clave:** *Cryptococcus neoformans/gattii*; meningoencefalitis; cirrosis; micosis; niños. (Fuente: DeCS, Bireme).

### Abstract

**Introduction:** In Colombia, cryptococcosis is a rare invasive fungal infection. **Objective:** To report the clinical case of a child with *Cryptococcus gattii* meningoencephalitis whose risk factor was immune dysfunction associated with cirrhosis, a risk factor described in adults which in the reviewed literature has not been reported in children. **Materials and methods:** A non-systematic review of the literature and a summary of the most relevant aspects of the clinical history were performed. **Results:** We present the case of a 16-year-old male patient with a history of cirrhosis who came for consultation with a clinical presentation of 8 days of fever, persistent emesis, frontal headache, photophobia and tinnitus. The physical examination did not present neurological alterations. In the study of cerebrospinal fluid, he presented positive direct molecular tests for *Cryptococcus neoformans/gattii* and the culture reported growth of *Cryptococcus gattii*. **Conclusions:** In this case, the importance of suspecting opportunistic infections in patients who have immunodeficiencies not only secondary to HIV infections, but also to those caused by other factors that alter the immune response such as cirrhosis is highlighted.

**Key words:** *Cryptococcus neoformans/gattii*; meningoencephalitis; cirrhosis; mycosis; child. (Source: DeCS, Bireme).

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## Introduction

One million cases of meningeal cryptococcosis are reported worldwide each year in patients with Acquired Immunodeficiency Syndrome (AIDS), half of which occur in Sub-Saharan Africa. Cryptococcosis mostly affects adult patient populations with AIDS, in contrast to pediatric populations<sup>(1)</sup>. In Colombia, 41 infants with cryptococcosis were reported between 1993 and 2010, representing an average annual incidence of 0.017 cases per 100,000 children younger than 16 years of age. AIDS is the most frequent risk factor reported in children with cryptococcosis, which affected 24.3% of the cases. Although multiple factors were reported, including autoimmune diseases as well as use of corticosteroids and prematurity, 46.3% of the pediatric population did not show any associated risk factor<sup>(2)</sup>. Based on our literature review, cases of pediatric patients with cirrhosis and meningoencephalitis caused by *Cryptococcus neoformans/gattii* have not been described. This is the reason why we report the clinical presentation, diagnosis, treatment and evolution of a patient with this unusual pathology. It is important to highlight that, as this is an infrequent event, it requires early diagnosis due to its high morbidity and mortality.

## Clinical case

The patient is a 16-year-old male from a rural area of the city of Cali, Colombia. He had chronic exposure to poultry excrement in his home and a history of idiopathic cirrhosis (class B Child-Pugh classification) that was documented three months prior to his hospital admission. This was the reason why he was waiting for a liver transplant in a level IV hospital facility. At the time of assessment in the emergency room, he displayed a clinical picture characterized by eight days of fever, persistent emesis, headache, photophobia and tinnitus. Consequently, a lumbar puncture was performed which obtained cerebrospinal fluid (CSF) with signs of (i) pleocytosis, (ii) hypoglycorrhachia, (iii) positive Chinese ink staining for fungal structures and (iv) positive molecular test for *Cryptococcus neoformans/gattii* through the *FilmArray™ Meningitis/Encephalitis panel* (Biomérieux, FilmArray™ 2.0, Marcy-L'Étoile, France) multiplex PCR (polymerase chain reaction) detection system. The results obtained from the cerebrospinal fluid sample are summarized in Table 1.

**Table 1.** Cytochemical analysis of the cerebrospinal fluid

	Diagnosis	10 days after the beginning of the treatment
Appearance	Slightly cloudy	Slightly cloudy
Glucose	21 mg/dl	34 mg/dl
Proteins	67 mg/dl	67 mg/dl
Leucocytes	15 cells/ml	128 cells/ml
PMN cells	95%	90%
Mononuclear cells	5%	105%
Chinese ink	Positive	Positive

A culture of the CSF sample showed growth of *Cryptococcus gattii* that was sensitive to Amphotericin B, 5-Fluocytosin and fluconazole. A CT scan of the skull was performed, where no cryptococcosis or signs of cerebral edema were identified. Antifungal treatment was initiated with Amphotericin B and 5-Fluocytosin, showing a good initial clinical evolution as demonstrated by the headache resolution, oral tolerance and resolution of other symptoms. Yet after ten days, the patient experienced clinical deterioration with signs of sepsis and digestive bleeding and this was the reason why he was transferred to the intensive care unit. The cytochemical control performed on the CSF showed hypoglycorrhachia, pleocytosis and evidence of fungal structures as revealed by the Chinese ink assay (Table 1). 24 days after his hospitalization, he presented with neurological deterioration, renal failure that required dialysis, ventilatory failure of central origin and coagulopathy with massive alveolar bleeding, which led to the death of the patient.

## Results

Members of the *Cryptococcus spp.* are round or oval yeast cells that have a 20 µm diameter. While *C. neoformans* has a universal distribution and can be easily found in the environment, mainly in soil contaminated with bird feces, *C. gattii* has been isolated from flowers and eucalyptus, ficus and almond trees<sup>(3)</sup>. Initially, it was thought that *C. gattii* was a subtype of *C. neoformans*, but now it is recognized as a unique species that is divided into four molecular types: VGI, VGII; VGIII and VGIV. The VGI and VGII strains have an endemic distribution in Australia, whereas VGII and VGIII are common in South America. VGIV strain is frequent in USA, where

it has been associated with aggressive meningoencephalitis<sup>(4)</sup>.

The course of the infection depends on three aspects: inoculum quantity, immunological status and virulence of the infecting strain. Regarding the virulence of this yeast, it is mainly determined by the presence of a capsule that inactivates the complement system, which in turn causes inhibition of phagocytosis, and the synthesis of the phenyl-oxidase enzyme that contributes to its neurotropism<sup>(4)</sup>. The portal of entry of *Cryptococcus* is lung alveoli, where cellular and humoral immune responses are normally triggered and executed to control the infection, a response mechanism that limits the infection in 90% of the cases. Resistance to the infection depends on the activation of macrophages and neutrophils by sensitized lymphocytes and the humoral response mediated by IgG and IgM opsonizing antibodies<sup>(5)</sup>. Given the fact that *C. gatti* infections have been described in a significant percentage of patients without risk factors, immunological factors that could be related to the susceptibility to this infection have been investigated. As a result, it was reported that 7 out of 30 patients (23%) had positive antibodies against granulocyte and macrophage stimulating factor<sup>(6)</sup>.

Cirrhosis was probably a risk factor for the patient to acquire the *C. gatti* infection. In this context, the “immune dysfunction associated with cirrhosis” is an immune disorder that has two components: (i) a persistent and inadequate stimulation of immune cells and (ii) immunodeficiency. These two elements make patients more vulnerable to opportunistic infections and elicit a poor response to vaccination. The factors related to secondary immunodeficiency are caused by opsonization defects, hypocomplementemia as well as chemotaxis and phagocytosis alterations<sup>(7)</sup>.

### Clinical manifestations

Generally speaking, the respiratory system is the portal of entry for this infection and the clinical manifestations can be so diverse that they range from an asymptomatic presentation to severe conditions characterized by continuous fever, pulmonary consolidation and respiratory difficulty that rapidly evolves into respiratory failure, which is known as fulminant pulmonary cryptococcosis. Although central nervous system infection is the most serious complication, its presentation is less symptomatic in the case of immunosuppressed patients<sup>(5)</sup>.

The most frequent symptom is headache that can be accompanied by other symptoms such as blurred vision, fever, chills, diaphoresis and nausea. In addition, papilledema, diplopia, altered state of consciousness, hallucinations, disorientation and irritability can be observed during the physical examination. Moreover, 1% of the patients may have cerebral cryptococcosis, cerebral edema and hydrocephalus. This is the main reason why it is mandatory to perform a cerebral nuclear magnetic resonance that is the most sensitive neuroimaging to rule out these types of complications<sup>(1)</sup>.

Another clinical manifestation is skin condition, which is characterized by lesions that have the form of papules, acneiform pustules or abscesses in immunocompromised patients. These manifestations can ulcerate over time and appear in the context of a disseminated disease in 15% of patients. Chancriform lesions have also been described in immunocompromised patients<sup>(5)</sup>.

### Diagnosis

The diagnosis of this disease can be achieved by the isolation of the yeast in culture, direct microscopic examination of the CSF sample or through biochemical and serological tests. Round or oval encapsulated blastoconidia can be observed through light microscopy of CSF preparations stained with Chinese ink. Other findings suggesting neuroinfection are high opening pressure, pleocytosis with predominance of lymphocytes, hyperproteinorrachia and hypoglycorrachia<sup>(1)</sup>. Differentiation between *C. neoformans* and *C. gattii* can be done with the canavanine-glycine-bromothymol blue assay, which is based on the fact that *C. gattii* degrades L-canavanine releasing ammonium that increases the pH of the media to greater than 5.8 values. This pH reduction is observed as a color change of the media from yellow to cobalt blue. Furthermore, conventional blood-based media promotes the growth of *Cryptococcus spp.* where this yeast forms characteristic cream-colored and mucoid-looking colonies.

The detection of capsular polysaccharides in cerebrospinal fluid by latex agglutination or ELISA has such a level of sensitivity and specificity to achieve a diagnosis efficiency of 93-100% and 93%-98%, respectively<sup>(8,9)</sup>. The *FilmArray™* meningitis/encephalitis panel of the automated detection system that uses a multiplex-nested PCR approach shows a high correlation for the diagnosis

of infectious encephalitis and meningitis. Although the least consistent results have been found for cryptococcal infections, this system seems to be more accurate for the diagnosis of *C. gattii* than the identification of *C. neoformans*<sup>(10)</sup>.

### Treatment

*C. gattii* and *C. neoformans*. infections are similarly treated. The management guide of the Infectious Diseases Society of America (IDSA) recommends that three aspects should be taken into account for the management of patients with CNS infections (Table 2). The first one is induction therapy, where treatment starts with antifungals such as polyenes and flucytosine, followed by suppressive regimens with fluconazole. The second key aspect is the early recognition of complications such as increased intracranial pressure as this is associated with high mortality. Finally, it is recommended to use amphotericin B in patients with renal impairment<sup>(11,12)</sup>.

Given the persistence of the infection after the induction phase, it is necessary to restart it and prolong it for 4 to 10 weeks. In case of relapse, it is recommended to treat the infection the same way as in the persistence stage and to evaluate isolated cultures for their susceptibility to antifungals in order to focus on disease management. Brain cryptococcosis that are located in accessible areas for resection and that are larger than 3 cm are recommended for surgical intervention and require induction therapy with Amphotericin B for six weeks, followed by consolidation therapy for 6-18 months<sup>(1,12)</sup>.

Some case series have reported that these patients could benefit from the use of dexamethasone<sup>(13)</sup>. In New Guinea, a retrospective study of patients with *C. gattii* infection described that people who received steroids experienced decreased vision loss and blindness, with improved vision reported in three patients<sup>(14)</sup>.

**Table 2.** Recommendations for the treatment of *Cryptococcus spp* meningoencephalitis<sup>(11)</sup>

Induction		Consolidation		Maintenance	
Primary scheme	Alternative scheme	Primary scheme	Primary scheme	Alternative scheme	
Amphotericin B 1 mg/kg/day	AnBd* 1 mg/kg/day	Fluconazole 400 mg/day	Fluconazole 200 mg/day	Itraconazole 200 mg/12 hr	
Fluocytosine 100 mg/kg/day	Fluconazole 800 mg/day	-	-	AnBd* EV 1 mg/kg/week	
Duration: 2 weeks	Duration: 4 - 6 weeks	Duration: 8 weeks	Duration: > 1 year	Duration: > 1 year	

AnBd\* Amphotericin B deoxycholate. Modified from Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2016;30(1):179-206.

### Conclusions

It is important to recognize opportunistic infections such as those caused by *C. neoformans/gattii* in patients who have immunodeficiencies, not only those associated with HIV but also those associated with other factors that weaken immune responses such as cirrhosis.

Infections caused by *C. gattii* that show a poor evolution should be treated in a timely matter to avoid complications such as intracranial hypertension, which could be prevented with repeated lumbar punctures in combination with antifungal treatment.

**Conflict of interests:** None.

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