SERIE DE CASOS

MENINGITIS POR CANDIDA ALBICANS EN PREMATUROS DEL SERVICIO DE NEONATOLOGÍA: REPORTE DE CASOS.

MENINGITIS DUE TO CANDIDA ALBICANS IN PREMATURE INFANTS IN THE NEONATOLOGY SERVICE: CASE REPORT.

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RESUMEN

Las infecciones por *Cándida* en la población neonatal son frecuentes considerando la edad del paciente y los factores de riesgo adicionales, pero la meningitis por el mismo germen es poco frecuente por la limitación para realizar un diagnóstico temprano y por los falsos negativos en el líquido cefalorraquídeo. Se presentan dos casos de pacientes en el área de Neonatología quienes inician con deterioro hemodinámico y crisis convulsivas por lo que se realiza abordaje, inicialmente por las características del líquido cefalorraquídeo en manejo con esquema antibiótico, pero ante el reporte de cultivo positivo a *Cándida albicans* se indica manejo específico, ambos con deterioro clínico progresivo y complicaciones múltiples, por lo que finalmente fallecen.

PALABRAS CLAVES: Meningitis Fúngica, Neonatología, Convulsiones, Líquido Cefalorraquídeo, Infectología.

ABSTRACT

Candida infections in the neonatal population are frequent considering the age of the patient and additional risk factors, but meningitis caused by the same germ is infrequent due to the limitation of early diagnosis and false negatives in the cerebrospinal fluid. We present two cases of patients in the Neonatology area who start with hemodynamic deterioration and convulsive crisis, so an approach is made,

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initially due to the characteristics of the cerebrospinal fluid in management with antibiotic scheme, but when a positive culture for Candida albicans is reported, specific management is indicated, both with progressive clinical deterioration and multiple complications, so they finally die.

KEYS WORDS: Meningitis Fungal, Neonatology, Seizures, Cerebrospinal Fluid, Infectious Disease Medicine

INTRODUCTION

The central nervous system (CNS) and its covering membranes can be involved in a variety of infectious processes, with devastating effects on structure and function.1 Infections can occur during intrauterine development, in association with the birth process, or in the first few postnatal days or weeks.1 Microbial organisms involved include several viruses, a protozoan (Toxoplasma gondii), a spirochete (Treponema pallidum), and numerous bacteria and fungi.1

Case 1

This is a preterm male patient of 30 weeks of gestation at the time of birth with a history of prenatal care on 14 occasions, 7 ultrasounds without reporting any problems, in the last control with the presence of blood pressure 140/100 mmHg, so it is decided to terminate the pregnancy via abdominal, obtaining a patient with bradycardia and inadequate respiratory effort for which orotracheal intubation was required, Apgar 6/8, somatometry with weight: 1150 gr, Height 37 cm. He is admitted to the neonatal intensive care unit presenting torpid evolution at the infectious disease level, with multiple approaches by the pediatric infectious disease service who requested blood and urine cultures, both positive for *Candida albicans*. Initially managed with liposomal Amphotericin B and later synergistic management with Fluconazole is added, which are administered for 13 and 6 days respectively. At 25 days of age and with 33.4 corrected weeks, the patient presented clinical convulsive seizures, starting treatment with Levetiracetam and performing a lumbar puncture (Table 1) as well as a transfontanellar ultrasound (Image 1) with evidence of dilation of the ventricular system; cerebrospinal fluid culture report also positive for *Candida albicans* (Table 2). The patient presented signs of septic shock, starting treatment with adrenaline and norepinephrine, requiring steroids for septic shock refractory to amines, but with no clinical response, so he died at 30 days of extrauterine life and with a corrected age of 33.1 weeks.

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Table 1. Cytological and cytochemical analysis of cerebrospinal fluid

Parameter	Result
Density	1009
Color	Xanthochromic
Glucose	100
Chlorides	129
Pandy	++
Cells	82 Neutrophils 31% Lymphocytes 44% Bands 1%
Proteins	546

Table 2. Cerebrospinal fluid culture report

Parameter	Result
Cerebrospinal fluid culture	*Candida albicans* Sensitivity: Caspofungin <0.12 S Voriconazole <0.12 S Mycofungin <0.06 S Fluconazole <0.05 S Amphotericin B 1 S

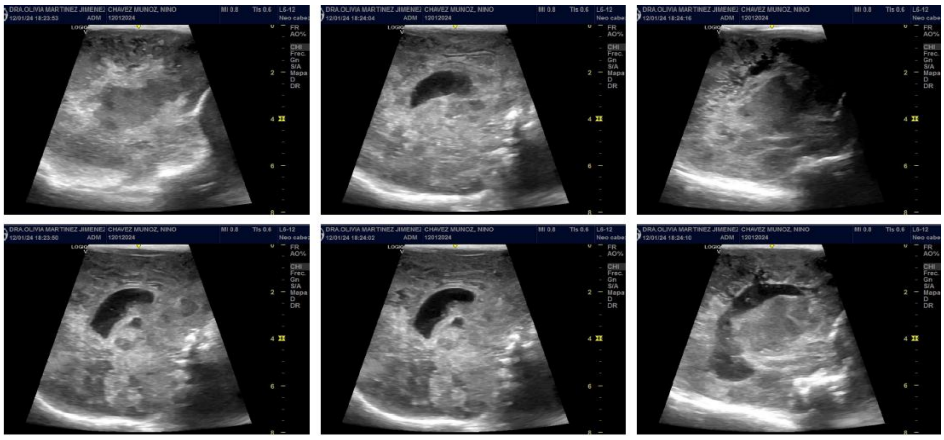

Image 1. Transfontanellar USG: Extensive areas of bilateral periventricular leukomalacia (white matter lesion with involvement of the periventricular zones). Asymmetrical increase in the amplitude of the ventricular system, within which multiple septa are identified.

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Case 2

A 29-week-old male patient, the product of pregnancy 2, had five prenatal visits and four normal ultrasounds. The delivery was performed via cesarean section due to fetal bradycardia, with evidence of premature abruption of the normally inserted placenta (30%) and a history of premature rupture of membranes 16 hours prior. A dose of surfactant was administered at the birth hospital, and antibiotic treatment with ampicillin and amikacin was initiated. Somatometry showed weight of 1195 grams, length 36 cm, Ballard score 29 weeks, and Apgar score 6/8. With a diagnosis of intestinal atresia, an exploratory laparotomy was performed, with evidence of IIA atresia, and fasting and total parenteral nutrition were indicated. However, at 30 days of life, with the presence of clinical seizures, treatment began with levetiracetam and an approach with lumbar puncture (Table 5) due to suspicion of meningitis, an antibiotic regimen with meropenem and vancomycin was indicated for 6 effective days; without an adequate response and evolution to septic shock managed with adrenaline. On physical examination, an increase in head circumference was assessed by neurosurgery, who performed an evacuating transfontanellar puncture with the same characteristics as the lumbar puncture and a positive culture for *Candida albicans* (Table 4), managed with Amphotericin and fluconazole. Despite management, the evolution was poor and the patient finally died at 1 month and 2 days of extrauterine life and 34 corrected weeks.

Table 3. Cytological and cytochemical analysis of cerebrospinal fluid

Parameter	Result
Density	1009
Color	Xanthochromic
Glucose	20.3
Chlorides	108
Pandy	+++
Cells	38 Neutrophils 82% Lymphocytes 12%
Proteins	735

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Table 4. Cerebrospinal fluid culture report

Parameter	Result
Cerebrospinal fluid culture	*Candida albicans* Sensitivity: Caspofungin <0.12 S Voriconazole <0.12 S Mycofungin <0.06 S Fluconazole <0.05 S Amphotericin B 1 S

DISCUSSION

Invasive candidiasis (Candida infections of the blood and other body fluids) is the second most common cause of infectious disease-related death in extremely premature newborns.

Despite antifungal treatment, 20% of patients who develop invasive candidiasis die, and neurodevelopmental impairment occurs in nearly 60% of survivors.1 Disseminated fungal infection in the newborn can cause meningitis, often with microabscesses.1

Although several fungi (e.g., *Cryptococcus, Coccidioides, and Aspergillus*) have been reported to cause meningitis, abscesses, or both in the newborn, the most common systemic infection is *Candida*, especially *Candida albicans* and, more recently, *Candida parapsilosis*, particularly in very low birth weight newborns.1

Candida meningitis is uncommon in children. 2 In one study, 2% of all positive cerebrospinal fluid cultures were fungal organisms, and Candida spp. accounted for 94.5% of fungal isolates. 2 Risk factors for positive cerebrospinal fluid Candida cultures in neonates include antimicrobial therapy, umbilical or peripherally inserted central catheterization, total parenteral nutrition, intubation, abdominal surgery, and prematurity. 2 In many cases of neonatal candidiasis, concurrent meningitis was not discovered until autopsy. 2 Extremely low birth weight newborns with Candida sepsis or meningitis are at increased risk of death or neurodevelopmental impairment. 2 Risk factors in children beyond the neonatal period included concurrent bacterial infection, chronic systemic or central nervous system disease, and the presence of central venous catheters. 2

Candida infections in very low birth weight newborns can be difficult to diagnose due to the wide range of symptoms. Most infants with disseminated candidiasis with meningitis present with respiratory distress and require supplemental

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oxygen, and most progress to require mechanical ventilation.3

Candida is often identified in endotracheal washings, urine, and blood of patients with Candida meningitis. Ophthalmologic examinations are very important to identify disseminated infections. Most patients present with temperature instability, elevated white blood cell counts, and feeding intolerance. Hepatomegaly may indicate systemic infection.3

The gold standard for the etiological diagnosis of meningitis remains cerebrospinal fluid culture. However, this test has a low sensitivity (48%),5 which can decrease to 20% if the patient received antibiotics before sampling. Furthermore, in newborns of 34 weeks' gestation or younger, 40% may have negative blood cultures, as do 50% of low-birth-weight newborns.6

Candida it is now the second most common organism isolated in cases of late-onset sepsis in very low birth weight infants. The judicious use of broad-spectrum antibiotics is an important preventive strategy.3 As 96% of positive blood cultures have grown within 48 hours and 98% within 72 hours, antibiotics should be discontinued after 2 to 3 days in most cases of suspected sepsis.3 Early introduction of enteral feedings can shorten the duration of parenteral nutrition, improve the infant's nutritional status, and reduce the need for intravascular access.3

Mortality from neonatal meningitis ranges from 20% to 50%, and is significantly higher in premature or very low-birth-weight infants.4 The presence of sequels in survivors is relatively frequent; these may be mild and not significantly interfere with the child's development, or severe and lead to serious limitations for their future.4

Mortality from systemic candidiasis is high. Up to 30% of cases are not diagnosed until autopsy, and delayed diagnosis is a major contributing factor to other deaths. Mortality from untreated disease is nearly 80%, and even with treatment, it reaches 60% in very low birth weight infants. Early diagnosis and empirical treatment in suspected cases are essential to reduce the mortality and morbidity of this condition.3

For non-neonatal patients, initial treatment for Candida meningitis is with liposomal amphotericin alone or in combination with oral flucytosine. Once the patient has responded, fluconazole is recommended if susceptible. Treatment should continue until signs, symptoms, and cerebrospinal fluid abnormalities have resolved. In neonates, amphotericin deoxycholate is initially recommended. Alternatively, liposomal amphotericin can be used.

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Once the newborn has responded to initial treatment, fluconazole can be used, and flucytosine can be considered as rescue therapy for newborns who have not responded to amphotericin therapy. However, it is difficult to use in low-birth-weight newborns and infants due to the immaturity of their gastrointestinal tract and the risk of developing necrotizing enterocolitis.

Voriconazole (VCZ) has excellent penetration into the central nervous system and is active against most Candida strains that cause infections at this level; however, clinical experience in newborns is too limited to recommend its use at this time.2 Caspofungin and the other echinocandins do not reach adequate concentrations in the CSF, but they do reach appropriate concentrations in the brain parenchyma and have been used successfully for treatment.2

In conclusion, we believe that early diagnosis is achieved through a comprehensive approach to the patient, taking into account their risk factors and comorbidities. Candida meningitis is not a common condition, but it should be considered in patients with risk factors and poor response to antibiotic treatment, all with the aim of avoiding or reducing short- and long-term neurological consequences.

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