Complications of systemic candidiasis in NICU

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Abstract

The aim of this study was to describe the complications of systemic candidiasis in newborns admitted to the Neonatal Intensive Care Unit (NICU) during a 10-year period. An observational study was carried out with 60 newborns admitted at the NICU from 1994 to 2003. The frequency of candidiasis was 1.8% and there was a predominance of male preterm newborns. Low birth weight occurred in 63.3% of the newborns, with 50% of them weighing <1500 g and among those, 23.3% weighed <1000g. The most frequent clinical findings were respiratory symptoms, temperature abnormalities, lethargy, hepatomegaly and splenomegaly. Candida *species identified were* C.albicans *(83.3%),* C. tropicalis *(6.7%),* C.parapsilosis *(5%) and* C.glabrata *(1.7%). There were complications in 85% of the cases: urinary tract infection (66.7%), pneumonia (56.7%), meningitis (13.3%), endocarditis (13.3%), deep venous thrombosis (10%), endophthalmitis (6.7%) and renal abscess (1.7%). The mortality rate was 33.3%. The authors concluded that the frequency of complications in systemic candidiasis was high, with lesions detected in several organs and systems, which probably contributed to the high mortality observed in the studied population. The results obtained show the importance of the systematic investigation of multisystemic complications in all newborns with a blood or sterile material culture positive for* Candida sp.

Keywords*: Systemic candidiasis - Neonatal sepsis; Candidaemia complications.*

INTRODUCTION

Systemic candidiasis has been increasingly diagnosed in Neonatal Intensive Care Unit (NICU), due to the increased number of very-low birthweight newborns and the use of more sophisticated technological resources in the treatment of these newborns. The mortality by Candida spp sepsis is high, varying from 25 to 54% of the cases, and it can reach 70% of very-low birthweight newborns[1], ranging from 20 to 40% when considering deaths that occurred within the first month of life[2,3]. Among the main risk factors are the use of broad-spectrum antibiotics, such as the third-generation cephalosporins and carbapenen, especially when two or more antibiotics are administered, gestational age below 28 weeks, mechanical ventilation, central venous catheter, parenteral nutrition, use of intralipids for more than 7 days, use of drugs such as histamine antagonists[4,5,6], teophyllin, corticosteroids, vasopressors, presence of gastrointestinal tract malformation and previous surgical procedure[7,8,9,10,11,12]. The clinical findings of systemic candidiasis are varied, with a usually insidious onset and signs and symptoms that can be mistaken for those observed in bacterial infections[1,13]. The multisystemic complications are frequent, due to the fungus capacity to promote tissue invasion in different organs such as the lungs, liver, spleen, heart, retina, brain and joints.[14,15,16,17]

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The exact incidence of severe complications such as meningitis, endocarditis and endoftalmitis in our country is unknown. The aim of this study was to describe the clinical findings and complications of systemic candidiasis in newborns admitted to the NICU during a 10-year period.

MATERIAL AND METHODS

An observational study was carried out with 60 newborns who had systemic candidiasis admitted at the NICU of the Children's Institute of Hospital das Clínicas of São Paulo's University Medical School from January 1994 to December 2003. Systemic candidiasis was defined as the presence of signs and symptoms of infection and the isolation of Candida spp in blood culture or normally sterile material culture: cerebrospinal fluid (CSF), urine (obtained through suprapubic puncture), articular fluid and peritoneal fluid. For the diagnosis of fungal pneumonia the following criteria were used: appearance of respiratory signs and symptoms and radiological pulmonary worsening in the presence of a positive Candida culture. All newborns admitted during the study period who presented systemic candidiasis were enrolled in the study. Newborns with a clinical picture compatible with fungal infection but no identification of Candida spp in the cultures and those who presented isolation from catheter tip only, were excluded from the study.

The analysis of the medical files was carried out. A protocol with the clinical data and laboratory assessment results was filled out for each patient. The variables analyzed were: gender, birth weight, signs and symptoms, thrombocytopenia (platelet count<100000/mm^3), thrombocytosis (platelet count >400000/mm^3), leukocytosis (leukocyte count>21000/mm^3), leukopenia (leukocyte count <5000/mm^3), eosinophilia (eosinophil count =10/ mm^3), complications and Candida species.

Chi-square test or Fisher's exact test were used to compare the frequency distribution of qualitative variables when the expected values were < 5. P values < 0.05 were considered statistically significant. The study was approved by the local Ethics Committee.

RESULTS

From January 1994 to December 2003, 3219 newborns were admitted at the NICU and 60 of them (1.8%) had a diagnosis of systemic candidiasis. The annual frequency of the disease varied from 0.8% in 1995 to 5.1% in 2002. There was a predominance of male preterm newborns (65%). Demographic characteristics of systemic candidiasis in 60 newborns, birth weight, clinical findings and complications are shown in tables 1 to 4, respectively. The Candida species identified were C. albicans (83.3%), C. tropicalis (6.7%), C. parapsilosis (5%) and C. glabrata (1.7%). Mortality rate was 33.3% (20 deaths) with a significant association between mortality and pneumonia (p<0.043) and mortality and thrombocytopenia (p< 0.014).

DISCUSSION

The frequency of systemic candidiasis (1.8%) was higher then those related recently by other authors who utilized the same diagnostic criteria used in our study. López Sastre and others[18], in a multicentric research with 20565 neonates admitted at NICU in Spain, reported systemic candidiasis in 0.57% and Linder and others[19], in Israel, reported the disease in 1.3% of 4201 newborns. The literature showed a variation of 2.2 to 12.9% in newborns with birth weight <1500 g and of 5.5% to 16.5% in newborns with birth weight <1000 g [20]. We observed systemic candidiasis in 23.3% and 26.7%, among newborns with birth weight <1000 g or <1500 g, respectively.

The main symptoms at the moment of suspected systemic candidiasis were respiratory alterations and fever (63.3%), similar to the study of Makhoul and others[21] that described fever in 42.8% of the 49 newborns with sepsis by Candida spp. Other findings observed by us included lethargy, hepatomegaly, thrombocytopenia, cardiac murmur and abdominal distension. The thrombocytopenia, observed in 46.7% of the patients showed a significant association with mortality rate. The decrease of platelet number has been pointed out by other authors in neonatal systemic candidiasis. Guida and others[22] compared 943 neonates with

Table1 - Demographic characteristics of systemic candidiasis in 60 newborns.

Variables	N	Mean	Median	Standard deviation	Minimum	Maximum
Age at admittance (1)	60	7.4	1.5	12.3	1	66
Age at disease onset (1)	60	31.5	24.5	21.2	8	120
Gestational age (weeks)	60	33.5	32	4.71	24	40
Birthweight (g)	60	1960	1512.5	1118.4	690	5000
Hospital stay duration (1)	60	67.9	60	37.3	16	210

(1) Days.

Table 2 - Birth weight in 60 newborns with systemic candidiasis.

Birth weight	N	%
<1000 g	14	23.3
1001-1499 g	16	26.7
1500-2499 g	8	13.3
≥ 2500 g	22	36,7
Total	60	100

gram-positive bacterial infections, gram-negative bacterial infections and fungal infections, and observed that the initial number of platelets was significantly lower in fungal sepsis, with a lower nadir, higher incidence and longer duration of thrombocytopenia. Similarly, Benjamin et al [23] showed that fungal sepsis is associated with a higher degree of thrombocytopenia when compared to sepsis by coagulase-negative Staphylococcus. Warris, Semmekrot e Voss [24] carried out a study in 24 premature with sepsis, with 8 cases of candidemia and 16 with bacterial sepsis; all cases of sepsis by Candida sp presented thrombocytopenia whereas only 50% of the bacterial sepsis group did.

Little is known about the complications of candidiasis in Brazil, with few studies having reported their real incidences. In the USA, a meta-analysis reported the following rates of mean prevalence: 15% of meningitis, 4% of brain abscess and ventriculitis, 5% of endocarditis, 3% of endophtalmitis, 5% of renal abscess and 1% of liver or spleen abscess[25]. We observed complications in different organs or systems in the 85% of the patients, as was expected, considering the severity of the fungal infection in the newborns. The main complication was urinary tract infection (66.7%), which is in agreement with other authors that point out the importance of the urinary system involvement in sepsis by Candida spp. The infection can manifest as fungal mycetoma and obstructive uropathy [26,27]. Renal abscess was observed in only one (1.7%) neonate in our study. Makhoul and others [21] reported renal abscesses in 7.1% of the cases. Congenital urinary system malformation, observed in 5% of our patients, and myelomeningocele with neurogenic bladder (7% of our patients) constitutes additional risk factors for urinary fungal infection.[28,29,30]

Pneumonia was the second more frequent complication, observed in 56.7% of the newborns. The significant association between pneumonia and death suggests that this complication contributed to the worsening of the candidiasis prognosis. The diagnosis of pneumonia by Candida presents difficulties, as the fungus isolation from tracheal secretion is not indicative of fungal pneumonia,

Table 3 - Clinical signs and symptoms of systemic candidiasis in 60 newborns.

Signs and Symptoms	N	%
Pulmonary stridor	38	63.3
Radiological pulmonary worsening	36	60.0
Tachypnea	24	40.0
Fever	38	63.3
Hypothermia	33	55.0
Lethargy	33	55.0
Hepatomegaly	31	51.7
Thrombocytopenia	28	46.7
Cardiac murmur	27	45.0
Abdominal distension	24	40.0
Splenomegaly	20	33.3
Apnea	17	28.3
Bradychardia	14	23.3
Jaundice	14	23.3
Skin Moniliasis	12	20.0
Increase of cardiac area at RX	10	16.7
Feeding refusal	9	15.0
Vomiting	8	13.3
Seizures	8	13.3
Petechiae	8	13.3
Digestive bleeding	7	11.7

Table 4. Complications of systemic candidiasis in 60 newborns.

Complications (1)	N	%
Urinary infection	40	66.7
Pneumonia	34	56.7
Thrombocytopenia	28	46.7
Meningitis	8	13.3
Endocarditis	8	13.3
Superior vena cava thrombosis	6	10.0
Endophtalmitis	4	6.7
Renal abscess	1	1.7

(1)Present in 51 (85%) newborns.

and it can mean only the colonization of the respiratory tract. Most of the neonates in our study needed prolonged tracheal intubation, and it is likely that the presence of this risk factor contributed for the ocurrency of infection. Other authors described an increased frequency of pneumonia in NICU, using diagnostic criteria similar to those utilized in our study. Romero Reyes and others [1] reported a radiographic image of bronchopneumonia in 57% of the patients with candidiasis. Chowdhary and others [31] diagnosed respiratory failure in 62.5% of 16 neonates with candidemia by Candida tropicalis. Pneumonia by Candida can occur following the aspiration of infected vaginal secretion by the fetus during delivery, or through hematogenic or embolic transmission. Mazor and others [32] described a preterm neonate who needed mechanical ventilation and a radiological image of pneumonia born to a woman with an asymptomatic infection of the amniotic fluid by Candida sp.

Meningitis occurred in 13.3% of our cases, being the identification of Candida spp in CSF a rare event. The central nervous system malformation or ventriculoperitoneal derivation are risk factors for fungal meningitis. We observed that 12.5% of the neonates with meningitis presented hydrocephalus with ventriculoperitoneal derivation. Among 8 neonates with abnormal CSF exam, only 3 (37.5%) had Candida in the CSF culture, confirming the difficulty of establishing a meningitis diagnosis through a CSF culture [33]. We agree with the authors who recommend consider as fungal meningitis any CSF abnormality in neonates with a positive blood culture for fungus. On the other hand, Fernandez and others [34], in a retrospective study of 106 neonates, detected meningitis in 21.7% of the patients, with a positive CSF culture in 74% of the cases.

Before the advent of echocardiography, endocarditis was considered a rare disease. Risk factors for this complication are congenital cardiopathy and central venous catheter. Among our patients, endocarditis ocurred in 13.3% of the cases. None of them had a congenital cardiopathy. Krebs and others [35] reported a 11-day-old newborn with endocarditis associated to multiple congenital malformations and central venous catheterism. Pacheco-Rios and others [36], in a retrospective study, reported 15 cases (13.6%) of endocarditis by Candida spp. in Mexico. All patients had a central venous catheter and 20% of them had a congenital cardiopathy. Vricella and others [37] described a infant with right ventricular obstruction and cardiocirculatory collapse caused by a vegetating fungal mass. Linder and others [38] described a 24-week preterm infant with a cardiac mass in the right atrium. Daftary, Palote e Whitehall [39] reported four cases of intracardiac fungal mass in extremely preterm infants that were treated surgically, who died despite treatment with 6 mg/Kg/day of liposomal Amphotericin. Divekar, Rebekya e Soni [40] reported endocarditis in a preterm infant with aortic stenosis and sepsis by Candida parapsilosis. Deep venous thrombosis occurred in 10% of the newborns in our study, being a quite high incidence, considering that the thrombosis of large vessels is rare in the neonatal period. Other authors reported an even higher frequency of thrombosis than that observed by us. Noyola and others [17], observed thrombus or vegetation in 15.2% of 65 neonates with candidiasis. This finding implies that the presence of the catheter associated to the fungal infection resulted in an endothelial lesion, fibrin deposit and thrombus formation.

Endophtalmitis, observed in 6.7% of the newborns, is reported from 0% [41] to 50%[14] of the neonates with systemic candidiasis. The lesion can manifest as a round, white, cotton-like formation, that fluctuates in the vitreous humor[15]. The frequency observed by us was similar to that of Noyola and others [17], who described endophtalmitis in 6% of 67 neonates with candidiasis within a 10-year period. Some authors have described the association between fungal corioretinitis and retinopathy of prematurity. The need for surgical procedure for the retinopathy is significantly higher among the newborns with candidemia, suggesting that ocular involvement is more severe among these neonates[42]. Gago, Capone e Trese [43] described a stage 3 retinopathy of prematurity and endophtalmitis by Candida in a preterm infant with a gestational age of 23 weeks. On the other hand, Karlowicz and others [44] studied 449 preterm infants whose birthweight was <1000 g, and concluded that candidemia was not an independent risk factor for the development of retinopathy of prematurity.

We conclude that the frequency of complications in systemic candidiasis was high, with lesions detected in several organs and systems, which probably contributed to the high mortality observed in the studied population. The results obtained show the importance of the systematic investigation of multisystemic complications in all newborns with a blood or sterile material culture positive for Candida sp.

Complicações da candidíase sistêmica em UTI neonatal

Resumo

O objetivo deste estudo foi descrever as complicações da candidíase sistêmica em recém-nascidos admitidos na Unidade de Terapia Intensiva Neonatal (UTIN), durante um período de 10 anos. Um estudo observacional foi realizado com 60 recém-nascidos admitidos na UTIN 1994-2003. A freqüência de candidíase foi de 1,8% e houve um predomínio do sexo masculino recém-nascidos prematuros. Baixo peso ao nascer ocorreu em 63,3% dos recém-nascidos, com 50% deles com peso inferior a 1500 gramas, e dentre esses, 23,3% pesaram <1000g. Os achados clínicos mais freqüentes foram os sintomas respiratórios, anormalidades na temperatura, letargia, hepatomegalia e esplenomegalia. As espécies de *Candida* identificadas foram *C.albicans* (83,3%), *C. tropicalis* (6,7%), *C.parapsilosis* (5%) e *C.glabrata* (1,7%). Ocorreram complicações em 85% dos casos: infecção do trato urinário (66,7%), pneumonia (56,7%), meningite (13,3%), endocardite (13,3%), trombose venosa profunda (10%), endoftalmite (6,7%) e abscesso renal (1,7%). A taxa de mortalidade foi de 33,3%. Os autores concluíram que a freqüência de complicações por candidíase sistêmica foi alta, com lesões detectadas em vários órgãos e sistemas, o que provavelmente contribuiu para a alta mortalidade observada na população estudada. Os resultados obtidos mostram a importância da investigação sistemática de complicações multissistémicas em todos os recém-nascidos que tenham cultura positiva para *Candida* sp.

Palavras-chave: Candidíase sistêmica – Sepse neonatal; Candidemia - Complicações.

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