NEONATAL CANDIDA INFECTIONS IN AN INTENSIVE CARE UNIT : A THREE YEAR EXPERIENCE

Hülya Bilgen, M.D.* / Eren Özek, M.D.* / Nurver Ülger, M.D.**
Nilgün Çerikcioğlu, Ph.D. / Güner Söyletir, M.D.****

* *Sub-department of Neonatology, Department of Pediatrics, School of Medicine, Marmara University, İstanbul, Turkey.*

** *Department of Microbiology, School of Medicine, Marmara University, İstanbul, Turkey*

ABSTRACT

Objective: Although technological advances in neonatal care increase survival rate in premature babies, they also contribute to the increasing incidence of systemic candida infections in this population. Therefore, we aimed to evaluate cases with systemic candida infections and discuss the results.

Methods: Eighteen neonates with disseminated candidiasis were evaluated according to their risk factors, culture results and antifungal susceptibilities.

Results: Fourteen out of eighteen were preterms and eleven of them weighed less than 1500 grams. The *Candida* species isolated from blood, urine or cerebrospinal fluid were Candida albicans in nine (50%), Candida parapsilosis in six (33%), Candida spp. in two (11%) cases and Candida pseudotropicalis in one (6%) case.

Antifungal susceptibility of the isolates to amphotericin B (AMB) and fluconazole (FCZ) was determined using the macrodilution method. Four of our patients received AMB while FCZ was started in fourteen cases but only ten of them showed good clinical and mycological response. In four patients the treatment was continued with AMB because of poor clinical response although only one of them had a high minimal inhibitory concentration level to FCZ. All of our patients were treated successfully without any complication.

Conclusion: Early recognition and treatment of infants with systemic candida infection will reduce morbidity and mortality. Identifying the Candida species and determining their susceptibility may be useful in planning the treatment of neonatal candidemia.

Key Words: Newborn, Systemic candidiasis

INTRODUCTION

In connection with continuous progress in neonatal intensive care units, systemic candida infections, previously considered to be a rare complication, are now frequently diagnosed in infants receiving intensive care (1). The incidence is as high as 2-5 % of very low birthweigt infants in a neonatal care unit (2). Disseminated candida infection is associated with prematurity, low birth weight, prolonged hospital stay, use of broad-spectrum antimicrobial agents and / or corticosteroids and / or theophylline, central vascular catheters, parenteral hyperalimentation, intralipid infusions and prolonged endotracheal intubation (1).

(Accepted 25 July, 2000)

Marmara Medical Journal 2000;13(4):201-204

The aim of our study is to evaluate the cases with systemic neonatal candidiasis diagnosed and treated in our neonatal intensive care unit.

MATERIAL AND METHODS

This hospital-based and retrospective study was undertaken on neonates with systemic candida infection over a three-year period between 1995 and 1997. According to the protocol in our unit, cultures were obtained from blood, urine (with catheter) and cerebrospinal fluid (CSF) in all cases with suspected sepsis. Culture positive specimens were evaluated according to standard guidelines (3). For the detection of the species, conventional methods and Candi-Fast tests were performed (International Microbio®). Antifungal susceptibility of the isolates to amphotericin B (AMB) and fluconazole (FCZ) was determined using macrodilution method following "The National Committee for Clinical and Laboratory Standards" (NCCLS) guidelines (4). FCZ of 6 mg/kg/d was started as the first choice of initial therapy when Candida septicemia was suspected based on the presence of risk factors and clinical signs (feeding intolerance, lethargy, etc.) for candida infection. According to the clinical response and the results of antifungal susceptibility studies, FCZ was either continued or changed to AMB. If continued, the duration of treatment was 2 weeks after a sterile culture. AMB was started with a test dose and administered in a graduated dose (0.25 mg/kg/d) up to a maximal dose of 1.0 mg/kg/d, given intravenously over a period of four to six hours. AMB was continued until a cumulative total dose of 20 mg/kg reached. Liposomal AMB was started with a dose of 1 mg/kg/d. According to our protocol, patients were routinely monitorized with serum biochemistry for drug toxicity.

Fundoscopic examination was performed on all babies with systemic candidiasis to detect endophthalmitis. They were also routinely evaluated with cranial and renal ultrasonography.

RESULTS

Eighteen neonates (9 females, 9 males) were diagnosed as having systemic candidiasis based on clinical suspicion with positive cultures obtained from the blood, CSF or urine. Fourteen cases had a gestational age of less than 37 weeks and eleven of them weighed less than 1500 grams. Mean birth weight and gestational age of cases were 1689 ± 197 grams (range 776-3500 grams) and 31.6 ± 1.1 (range 26-40 weeks), respectively. The features of the cases are shown in Table I.

Hypoactivity, lethargy, poor feeding and apnea were the most common presentations. The infection was associated with prolonged antibiotic therapy and hyperalimentation with intravenous fat emulsion (18/18), intubation (15/18), arterial (13/18) and central venous (12/18) catheterization and theophylline use (11/18). Three babies (two meningomyelocele, one congenital heart disease) had congenital anomalies.

Candidiasis was diagnosed at a mean age of 22 ± 2 days. The Candida species isolated from blood, urine or cerebrospinal fluid were Candida albicans in nine (50%), Candida parapsilosis in six (33%), Candida spp. in two (11%) cases and Candida pseudotropicalis in one (6%) case. Antifungal susceptibility of the isolates to AMB and FCZ is shown in Table II. For case number 4-6-12 and 15, the same organisms were isolated from blood, urine or CSF. The results revealed that all the isolates were susceptible to AMB while all but one of the isolates were susceptible to FCZ. The patient (case no. 6) with a high MIC of FCZ (> 100 mg/l) did not clinically respond with persistant positive blood cultures to 6mg/kg/d FCZ during two weeks of treatment.

Therapy was started with AMB in four patients. Fourteen cases received FCZ but only ten of them showed good clinical and mycological response. In four patients the treatment was continued with AMB because of poor clinical response although only one of them had a high minimal inhibitory concentration level to FCZ. Liposomal AMB was used in two cases. All patients except one, were treated successfully without any complication. One baby died unrelated to a systemic fungal infection after 18 days, completing a successful course of treatment.

Fundoscopic examinations of all babies were normal. Hydrocephaly was detected in two babies with meningomyelocele. Renal fungus

Table I. Features of cases with candidemia in NICU patients

Case No	Birthweight (grams)	Gestational age (weeks)	Gender	Neonatal problems	The postnatal age at diagnosis (d)
1	1700	30	F	Prematurity + LBW† + Convulsions + Apnea + IVH°	18
2	1458	30	F	Prematurity + VLBW‡ Apnea	22
3	3500	40	M	Septicemia + Congenital heart disease + Met. Acidosis	35
4	1470	34,5	M	Prematurity + VLBW + RDS¶ +Septicemia + §DIC	26
5	1258	29,5	F	Prematurity + VLBW + Septicemia	25
6	1040	27	F	Prematurity + VLBW	15
7	1200	28	M	Prematurity + VLBW + Septicemia + Ventriculitis + IVH	15
8	1250	29	F	Prematurity +VLBW	15
9	880	26	F	Prematurity +VLBW + RDS + Septicemia	21
10	2800	37	F	Pneumonia + Septicemia	21
11	776	26	M	Prematurity + VLBW +RDS	32
12	1800	33	M	Prematurity + Septicemia + Ventriculitis + Osteomyelitis	38
13	1900	33	M	Prematurity + LBW + PDAµ + Septicemia	9
14	1390	33	M	Prematurity + LBW + RDS + Septicemia	22
15	1044	28	F	Prematurity + VLBW + RDS	34
16	934	27	F	Prematurity + VLBW + Septicemia	13
17	3500	39	M	Myelochisis + Hydrocephalus + Ventriculitis	21
18	2300	39	M	Myelochisis + Hydrocephalus	17

F: Female, M: Male, †LBW: Low birth weight, ‡VLBW: Very low birth weight,
°IVH: Intraventricular hemorrhage , ¶RDS: Respiratory distress syndrome,
µPDA: Patent ductus arteriosus, §DIC: Disseminated intravascular coagulation

Table II. *MIC values for Candida species

Case No	Organism isolated	Site(s) of isolation	Amphotericin B (MIC µg/l)	Fluconazole (MIC µg/l)
1	C. parapsilosis	Urine	0.16	3.12
2	C. parapsilosis	Urine	0.16	3.12
3	C. parapsilosis	Blood	0.31	0.78
4	C. parapsilosis	Blood+Urine	0.08	0.78
5	C. albicans	Blood	0.62	0.19
6	C. albicans	Blood+Urine	0.62	>100
7	C. albicans	Blood	0.62	0.78
8	C. pseudotropicalis	Urine	0.16	0.78
9	C. parapsilosis	Blood	1.25	1.56
10	C. papasilosis	Blood	0.62	0.19
11	C. spp	Blood	0.25	1
12	C. albicans	Blood+Urine+CSF**	0.25	1
13	C. albicans	Blood	0.25	1
14	C. albicans	Blood	0.5	1
15	C. spp	Blood+CSF	0.25	0.5
16	C. albicans	Urine	0.125	0.25
17	C. albicans	Blood	0.125	0.25
18	C. albicans	Urine	0.25	0.5

* MIC: minimal inhibitory concentration
** CSF: cerebrospinal fluid

ball was not present in the study group.

DISCUSSION

Technological advances in neonatal care have increased survival rates in premature babies, but have also contributed to the increasing incidence of systemic candida infection in this population (1). Clinical manifestations vary and are indistinguishable from other pathogens. As the signs and symptoms of infection are insidious, a high suspicion index is needed to diagnose fungal infection. Hypoactivity, lethargy, poor feeding and apnea were the most common presentations in our cases.

Fungal septicemia should be strongly considered in an infant weighing less than 1500 grams who has been hospitalized for a prolonged period, is receiving parenteral nutrition through a central vascular catheter and has previously been treated with broad-spectrum antibiotics and/or theophylline. Presence of congenital anomalies

(congenital heart disease, meningomyelocele, omphalocele, etc.), a history of gastrointestinal tract disease (i.e. necrotizing enterocolitis) or invasive procedures such as intubation and surgery are other important risk factors for candida septicemia (5).

In our study group, 61% of the cases weighed less than 1500 grams. The most common risk factors were prolonged antibiotic therapy and hyperalimentation, followed by intubation, arterial and central venous catheterization and theophylline use. Three babies (two meningomyelocele, one congenital heart disease) had congenital anomalies as well.

In general, systemic candida infections in preterm neonates occur at a mean age of 1 month. In our study group, systemic candida infection was diagnosed at a mean age of 22 ± 2 days. Standard neonatal systemic antifungal therapy is AMB alone or in combination with 5-fluorocytosine. However, this treatment modality can be associated with toxicity and especially the need for prolonged venous access. Although it has been reported that liposomal AMB which is a new alternative to conventional AMB in neonates has less side effects, its high cost limited its use in our nursery (6, 7). FCZ has also been effective in the treatment of fungal septicemia in the neonatal population (6, 8). In our nursery, because of its low cost and toxicity and excellent penetration into the cerebrospinal fluid, FCZ was chosen initially when systemic candida infection was suspected because Amphotericin B was not available in Turkey during this period (9). Ten out of 14 neonates were treated successfully with FCZ. Although 3 out of 4 had a low MIC level, clinical response to FCZ was not obtained. This result suggested that in vivo activity and in vitro susceptibility to these antifungals are not correlated and still needs further investigation.

We have not seen any side effects neither with AMB nor with liposomal AMB, although several studies have demonstrated that liposomal AMB is far less toxic then the conventional drug (7, 10). In our study group, none of the babies died because of systemic candida septicemia although current mortality rates reported in the literature, range from 18% to 50% (1).

We conclude that early recognition depending on the most common risk factors and presentations such as feeding intolerance, lethargy or apnea and promt treatment has resulted in this favorable outcome. Identifying the Candida species and determining their susceptibility may be useful in planning the treatment of neonatal candidemia.

REFERENCES

1. *Ng PC. Systemic fungal infections in neonates. Arch Dis Child 1994; 71: 130-135.*
2. *Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low birthweight infants: clinical manifestations and epidemiology. Pediatrics 1984; 73: 144-152.*
3. *Jones JM. Laboratory diagnosis of invasive candidiasis. Clin Microbiol Rev 1990; 3: 32-45.*
4. *National Committee for Clinical Laboratory Standards: Reference method for broth dilution intifungal susceptibility testing for yeasts. Proposed Standard Document M. 27. P. NCCLS, Villanova, PA. 1992.*
5. *Faix RG, Kovanik SM, Shaw TR, Johnson RV. Mucocutaneous and invasive candidiasis among very low birth weight (<1500 grams) infants in intensive care nurseries: a prospective study. Pediatrics 1998; 83: 101-107.*
6. *Driessen M, Ellis JB, Cooper PA, et al. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. Pediatr Infect Dis J 1996; 15: 1107-1112.*
7. *Driessen M, Ellis JB, Muwazi F, De Villiers FP. The treatment of systemic candidiasis in neonates with oral fluconazole. Ann Trop Paediatr 1997; 17: 263-271.*
8. *Scarcella A, Pasquariella MB, Giugliano B, Vendemmia M, de Lucia A. Liposomal amphotericin B treatment for neonatal fungal infections. Pediatr Infect Dis J 1998; 17: 146-148.*
9. *Cruciani M, Di Perri G, Molesani M, Vento S, Concia E, Basetti D. Use of fluconazole in the treatment of Candida albicans hydrocephalus shunt infection. Eur J Clin Microbiol Infect Dis (Letter) 1992; 11: 957.*
10. *Lackner H, Schwinger W, Urban C, et al. Liposomal amphotericin-B (AmBisome) for treatment of disseminated fungal infections in two infants of very low birth weight. Pediatrics*