Central Nervous System Candidiasis Presenting with Persistent Brain Parenchymal Microabscess in a Premature Infant

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Candidal meningitis is a serious complication of systemic candidiasis and cause of major morbidity and mortality. This is especially true in very low birth weight premature infants. We describe a premature neonate who suffered from systemic candidal infection with brain parenchymal involvement detected by cranial ultrasound. This patient survived after antifungal treatment but delayed neurodevelopmental outcome was noted in the subsequent follow-up. Physicians should be more alert to the early diagnosis of fungal infection in premature babies as central nervous system candidal infection can result in neurodevelopmental delay in such infants. *(Chang Gung Med J 2006;29(4 Suppl):29-34)*

Key words: central nervous system candidiasis, very low birth weight infant, brain parenchymal microabscess.

Systemic candidiasis is a common disease with an incidence of 3% to 5% and usually causes a high mortality and morbidity in very low birth weight (VLBW) premature infants.[1,2] Due to improvements in the equipment and therapeutic strategies of neonatal intensive care, candidal infection has an increased incidence of improved survival rates among VLBW premature neonates.[3] Central nervous system (CNS) involvement is a serious complication of disseminated candidiasis. Here we describe a premature neonate who suffered from *Candida albicans* fungemia complicated with CNS parenchymal involvement. This patient survived after antifungal treatment but delayed neurodevelopmental outcome was detected in the subsequent outpatient clinic follow-up.

CASE REPORT

A male baby born at gestational age of 29 weeks with a birth weight of 1290 gm and Apgar scores of 7 and 9 at 1st and 5th minutes, was admitted to our intensive care unit immediately after birth due to respiratory distress. The mother was gravida 2, para 2 and had no medical history of maternal fever or administration of antenatal steroids or antibiotics. Physical examination of the baby was unremarkable except for the presence of subcostal retraction. The initial impression was respiratory distress syndrome and the symptoms improved the next day after oxygen supplementation. Empirical antibiotic treatment with ampicillin and gentamicin was prescribed after admission. Though the body temperature had appeared unstable from the 5th day, antibiotics were discontinued on the 7th day due to negative blood and urine culture results. A peripheral intra-central catheter was inserted on the 5th day for parenteral nutrition, while enteral feeding was also gradually increased.

Unfortunately, sepsis was strongly suspected on

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the 11th day because of frequent bradycardia with desaturation and unstable body temperature. Intubation with mechanical ventilator support was performed. Antibiotics were applied after septic work-ups that included analyses of blood and urine, cultures of blood and urine, and chest radiography. The white blood cell count was 13100/cu mm (segments 84%, lymphocytes 6% and monocytes 10%) and the C-reactive protein was within normal limits. The cerebrospinal fluid (CSF) examination, including routine and biochemistry studies, was also within normal limits (cell count was between 0 to 5 /mm^3, glucose 42 mg/dL and protein 55 mg/dL). CSF cultures were negative for both bacteria and fungus. Three days later, the blood culture revealed the growth of *Candida albicans*. Amphotericin B was immediately prescribed with an initial dose of 0.25 mg/kg intravenously, increasing by 0.25 mg/kg/day until the dose of 1 mg/kg/day was reached.

Cardiac and renal echography were performed for systemic fungal infection survey and both revealed negative results of vegetation and/or fungal ball formation. The brain sonography performed four days after birth was unremarkable. However, a follow-up brain echo one week after fungemia showed multiple microabscesses scattered in the bilateral basal ganglion and periventricular white matter (Fig. 1). Under the impression of CNS candidal infection, fluconazole was added with a loading dose of 10 mg/kg and 6 mg/kg/day intravenously for maintenance. Repeated blood and CSF cultures after antifungal treatment for two weeks were negative. The total treatment course was one month for fluconazole and two months for amphotericin B (accumulated dose of 58.5 mg/kg). Serial cranial sonography at one week, one month and two months after the onset of fungemia still presented with bilateral basal ganglia punctuated hyperechogenicity suggesting microabscess formation. For further intervention, brain magnetic resonance imaging (MRI) was arranged after completion of the treatment. The MRI demonstrated meningeal enhancement suggestive of inflammatory changes in the meninges (Fig. 2). The clinical condition improved gradually and the baby was discharged on the 93rd day of life.

The patient received regular follow-up at our outpatient department. Retinopathy of prematurity grade Ⅰ was diagnosed six weeks after birth and remained the same at subsequent examinations. The auditory brain stem response at the corrected ages of three and six months showed mild hearing impairment on the right side. The brain sonography six months and one year after discharge still revealed bilateral basal ganglia punctuated hyperechogenecity. At the corrected age of 1.5 years, the patient had delayed language development. His mental developmental index (MDI) and psychomotor developmental index (PDI) were below 1 to 2 standard deviations (SD) of the mean value. At the corrected age of 2 years, he still required support to walk. The Department of Rehabilitation assessed him as having delayed auditory comprehension and verbal expression.

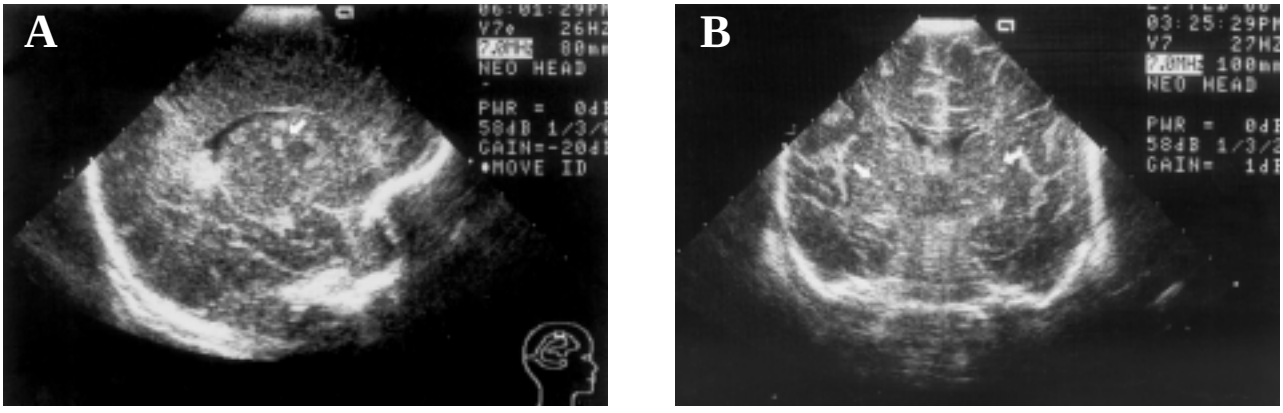

Fig. 1 Parasagittal (A) and coronal (B) cranial ultrasound views performed on the 25th day of life. Arrows indicate multiple hyperechoic microabscesses scattered in the brain parenchyma, including the bilateral basal ganglia and periventricular white matter.

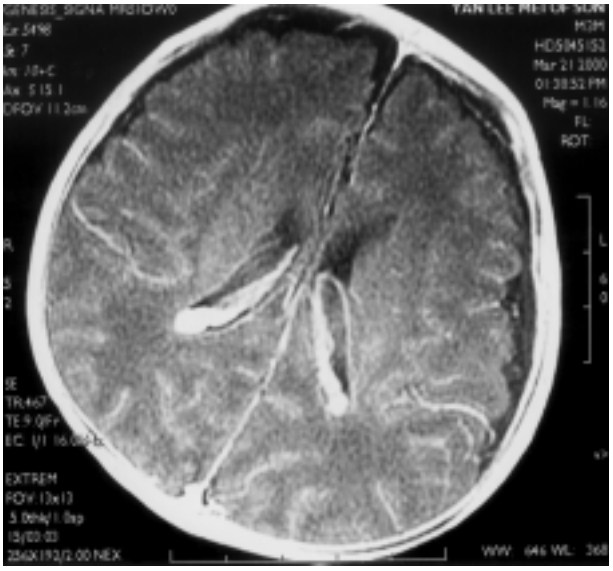

Fig. 2 Coronal view of contrast-enhanced T1-weighted magnetic resonance imaging (MRI) scan showing relatively increased meningeal enhancement surrounding both hemispheres reflecting inflammatory change. No abnormal brain parenchymal intensity presented.

DISCUSSION

Systemic candidiasis is an important cause of late onset sepsis in premature neonates and infants, especially in VLBW cases. It has an incidence rate of 3% to 5% in premature babies, with an average onset time of 33 days.[1,4] However, Melville et al. reported seven cases of early onset systemic Candida infection in 1996 and concluded that fungemia could occur in infants with a median age as young as seven days.[4] Our case presented with fungemia-associated symptoms at five days old, earlier than the average. Clinical manifestations of systemic candidiasis are usually nonspecific and subtle, including temperature instability, respiratory distress requiring ventilator support, abdominal distention, apnea and bradycardia, lethargy, and decreased perfusion, which can also be found in other types of infections.[5] It is very difficult to distinguish fungal infection from bacterial infection by clinical presentation alone. In our case, the temperature instability on postnatal day 5 may have been the first sign of systemic infection, followed by frequent bradycardia and apnea.

VLBW premature infants are one of the major groups at risk for systemic fungal infection.[4,6] The host risk factors include relative immunodeficiency, decreased neutrophil number and function, immature skin structure and cutaneous barriers, and the possibility of ascending infection in the uterus.[5] The nosocomial risk factors include the prolonged use of antimicrobials, central venous catheter placement, multiple invasive procedures, intralipid and parenteral nutrition use, intubation, and steroid administration.[4,6] The infant reported here apparently had some predisposing factors for candidiasis such as prematurity with VLBW, broad spectrum antibiotic use, intubation and central line placement with total parenteral nutrition use, which led to the systemic fungal infection.

Central nervous system candidiasis is a serious complication of systemic fungal infection, with an incidence of around 20% but is rarely diagnosed in the early stages of infection.[7] The rate of positive CSF culture is usually low because of slow growth and low concentration of fungi in the CSF.[1] In the past, definitive diagnosis of CNS fungal infection with negative CSF culture mainly depended on postmortem autopsy findings.[1] Recently, some studies applied imaging examinations, including cranial ultrasound and MRI, to aid in the early diagnosis of CNS involvement of systemic candidiasis.[1,8-11] Brain sonography can demonstrate disseminated hyperechoic lesions reflecting microabscesses in the brain parenchyma, mainly in subcortical, periventricular and basal ganglial areas.[1,8] Other findings included periventricular cavitation and hydrocephalus with echogenic debris.[11] Our case had persistent brain lesions consisting of multiple echogenic microabscesses over the periventricular and basal ganglial areas, a finding consistent with the earlier reports.[1,8] Use of MRI to detect CNS fungal infection, especially in VLBW infants, is rarely reported in the medical literature. In the study by Huang in 1998, MRI was used in one case that presented with disseminated brain parenchymal enhancing nodules and in another with leptomeningeal enhancement without evidence of parenchymal involvement.[1] In our case, time difference may be the reason for finding no nodular lesions on the MRI. However, the increased enhancement of the meninges and choroid plexus might indicate residual lesions caused by previous candidal meningitis. On the other hand, MRI still has its limitations in clinical application, particularly for the VLBW premature infant with unstable vital signs. In

recent studies, it was suggested that brain sonographic examination could be more valuable and more economical than MRI in the early diagnosis of CNS involvement in high-risk neonates and premature infants with systemic candidiasis.[1,8-11]

The conventional therapy for systemic candidiasis is amphotericin B alone or in combination with flucytosine.[12,13,16] However, the serious side effects of amphotericin B, particularly nephrotoxicity and hepatotoxicity, and the limited oral form prompted the search for an alternative treatment option. Recent studies claimed that fluconazole monotherapy was effective for disseminated fungal infection, including CNS involvement, because of its ability to penetrate the blood-brain barrier, as well as being available in both intravenous and oral preparations.[5,14-16] Amphotericin B remains the first line therapy for disseminated candidiasis. If fungemia persists or CNS involvement presents, the addition of fluconazole should be considered.[13-16]

There is no standard dose or treatment duration for candidal infection. The general accumulated dose of amphotericin B is from 25 mg/kg to 50 mg/kg and the dose of fluconazole is 5 or 6 mg/kg/day for eight days to three months.[17] In systemic candidiasis, treatment is discontinued when the blood cultures become sterile. For CNS candidal infection, medications should be continued until CNS involvement improves.[14-16]

Previous studies indicated that candidal infection of the CNS has a significant long-term impact on the neurodevelopmental outcome of patients.[1,8] Moreover, the prognosis of cerebral candidiasis is considered to be worse in patients with parenchymal involvement than in those with only ventricular involvement.[1,8] Our case was followed up until the corrected age of two years and delayed milestones with lower Bayley score (moderate delay, 1 to 2 SD below the mean) in association with hearing and language impairment were detected.

We conclude that systemic candidiasis is associated with increased short- and long-term morbidity in VLBW infants. The most important complication of fungal infection is CNS involvement. Brain sonography appears to be a quite sensitive and useful diagnostic tool. Early detection of brain parenchymal involvement might provide insights into the neurodevelopmental outcome of such patients.

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早產兒中樞神經念珠菌感染造成腦部實質微小膿瘍變化

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念珠菌腦膜炎是很嚴重的一種併發症，臨床上有很高的致病率及死亡率，尤其在極低體重的早產兒更爲明顯。本文報告一位全身性念珠菌感染的早產兒，在腦部超音波檢查中出現連續且長期的腦部實質變化。經過完整的抗黴菌藥物治療後，病患已痊癒出院，但在門診持續追蹤時，卻出現神經發育遲緩變化。所以在早產兒的病例中，念珠菌腦膜感染會大幅提高後續神經發育缺陷的機會，在臨床上要特別注意早產兒早期黴菌感染的診斷及治療。(長庚醫誌2006;29(4 Suppl):29-34)

關鍵字：中樞神經念珠菌感染，極低體重兒，腦部實質微小膿瘍。

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