Persistent Candida albicans Infection of A Cerebrospinal Fluid Shunt Infection Unresponsive to Amphotericin B Treatment Because of Increased Minimum Inhibitory Concentration

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Abstract

Infection is still the most common complication of shunt procedures in children. However fungal infection is considered to be rare, it is also associated with significant morbidity and mortality. The risk is increasing in premature neonates and after neurosurgery. Herein, we present a preterm neonate with persistant *Candida albicans* cerebrospinal fluid (CSF) shunt infection that was unresponsible to amphotericin B treatment due to increased minimal inhibitory concentration (MIC) during the therapy period and later which was treated by voriconazole plus flucytosine. *(J Pediatr Inf 2015; 9: 181-4)*

Keywords: *Candida albicans*, shunt infection, amphotericin B, minimal inhibitory concentration

Introduction

Use of cerebrospinal fluid (CSF) shunt devices is a common practice in neurosurgery, and infection due to the shunt is the most frequent complication. However, fungal infection is still considered to be rare. The clinical manifestations are subtle and insidious. The commonest fungal infection reported, of the central nervous system (CNS), is candidal meningitis (1). Herein, we present a case with persistant *Candida albicans* CSF shunt infection that could not be treated with amphotericin B due to increased MIC during the therapy then by switching antifungal agents to voriconozole and flucytosine, infection was treated successfully.

Case Report

A three-month-old boy was referred to our hospital with the following history: He was born prematurely at 32th week of gestation by cesarean section. On the first postnatal day he had been hospitalized and stayed for 22 days because of respiratory distress syndrome and prematurity. He underwent ventriculo-peritoneal (V-P) shunt due to hydrocephalus caused by intraventricular hemorrhage. After discharge, 30 days later he had been hospitalized in another hospital because of fever. Shunt infection had been considered there. Broad spectrum antibiotic treatment had been first initiated and V-P shunt had been removed and external ventricular drainage had been inserted at that time. Antimicrobial treatment had been replaced by fluconazole plus caspofungin in order that *C. albicans* had been isolated from CSF culture. Despite the treatment *C. albicans* had continued to be isolated from several CSF cultures. Antifungal treatment had been replaced with amphotericin B deoxycholate because MIC of amphotericin B was <1 mcg/mL for *C. albicans.* On the 28th day of therapy *C. albicans* was isolated from CSF culture again, so the patient was referred to our hospital.

During physical examination on admission to our hospital he appeared conscious, His temperature was 38.5°C. Laboratory tests revealed total leukocyte count of 13,400/mL, hemoglobin

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of 9.8 g/dL, platelet count of 382,000 /mL. Laboratory findings including for hepatic function tests, serum creatinin and electrolyte levels revealed normal limits. The CSF from drain contained protein of 41.47 mg/dL, glucose of <20 mg/dL against the blood glucose of 95 mg/dL. Urine, blood and CSF samples were taken for culture. Urine and blood samples were sterile. CSF gram stain showed rare leukocyte and the presence of clustered and branched pseudohyphae. Therefore, liposomal amphotericin B was initiated, but *C. albicans* was isolated from CSF culture again despite the treatment. Afterwards, intraventricular liposomal amphotericin B was added to intravenous liposomal amphotericin B. As MICs of amphotericin B and fluconazole for *C. albicans* that was yielded again were 2 mcg/mL, 1 mcg/mL, respectively, the treatment was replaced by voriconazole plus flucytosine. Hence any microorganisms were not isolated from CSF culture. The patient was successfully treated with a combination of voriconazole plus flucytosine for six weeks. After antifungal treatment V-P shunt was inserted and he was discharged from hospital.

Figure 1 shows his imaging findings on admission (1a) and after treatment (1b).

Discussion

Fungal infection is still considered to be rare, however, shunt infections caused by *Candida* have recently increased (ranging from 6% to 17%). Broad spectrum antimicrobial therapy, corticosteroids, and hyperalimentation, intravascular catheters, immunodeficiency may tend to develop shunt infection produced by fungus (2). Prematurity, former shunt infection, using neuroendoscopy are independent risk factors for shunt infection (3). Preterm newborns have immature immune systems which leads to reduce in capacity to adequately respond to infections. Although our patient didn't have a diagnosis as immunodeficiency syndrome, prematurity can be attributable to secondary immuncompromise status.

Candida meningitis can occur as a manifestation of disseminated candidiasis, which most often occurs in premature neonates, in the presence of ventricular drainage devices (1, 4). Chiou et al. (1) performed a retrospective study in 1994 and reported that all the shunt infections due to *Candida* species occurred in premature babies and the underlying factors were the neurosurgical procedures performed for the treatment of hydrocephalus.

In one review it is reported that, 77% of candida infections developed within three months of shunt manipulation, suggesting inoculation of the organism during surgery (5). Our patient was also stayed in hospital due to prematurity for 22 days. He underwent ventriculo-peritoneal (V-P) shunt due to hydrocephalus caused by intraventricular hemorrhage and he developed shunt infection 30 days after the surgery.

Meningitis is the most common clinical picture in central nervous system infection caused by *Candida.* However lots of small abscesses in the brain parenchyma, large solitary brain abscesses, and epidural abscesses have been observed in literature.

Candida albicans has been reported as the predominant isolate in all reports due to fungal shunt infections earlier (1, 6), followed by *Candida parapsilosis*. Other species of candida reported are *Candida tropicalis* and *Candida famata* (6).

Investigation and culture of ventricular fluid are essential to make a diagnosis; examination of lumbar CSF is not enough. There is usually pleocytosis. Increase protein level is more common than anormal glucose level in ventricular fluid (7). Our patient has a glucose concentration below 20 mg/dL, however protein concentration was 41.47 mg/dL.

CNS candidiasis has high mortality rate unless CNS candidiasis is treated. However mortality rate has been reported as 10-53% from small case series despite appropriate treatment (5). The therapy for fungal infection of a CSF shunt still consists of externalisation of the shunt, administration of systemic antifungal agents and placement of a new shunt and the elective regimen consists of amphotericin B intravenous (IV) and/or intraventricular (IVT) for a period of at least four weeks (8). We also used the combination therapy of externalisation of the shunt and administration of IV and IVT antifungal agent.

The incidence of C. albicans resistance is very low. An analysis of in vitro susceptibilities of approximately 90,000 isolates of C. albicans collected from 40 countries from 1997 to 2005 demonstrated that only 1.5 percent were resistant to fluconazole (9). The vast majority of *C. albicans* isolates are susceptible to amphotericin B. In 2012 Pfaller et al reported a study of 9,252 clinical isolates of *C. albicans*, 99.8% remained AmB sensitive (10). In the literature we could not find any resistance ratio for *Candida albicans* to amphotericin B.

Fluconazole achieves excellent level in CSF and brain parenchyma. Because of fluconazole therapy treatment failures have been observed in earlier studies it is not prefered as primary therapy. Fluconazole as initial therapy is used for those patients for whom amphotericin B is contraindicated.

Echinocandins are not recommended for CNS candidiasis because they do not achieve adequate CSF concentrations to treat Candida meningitis (11).

Before admission to our hospital our patient was treated with fluconazole and caspofungin but we stopped that therapy because of the cultures that still growing *C. albicans*.

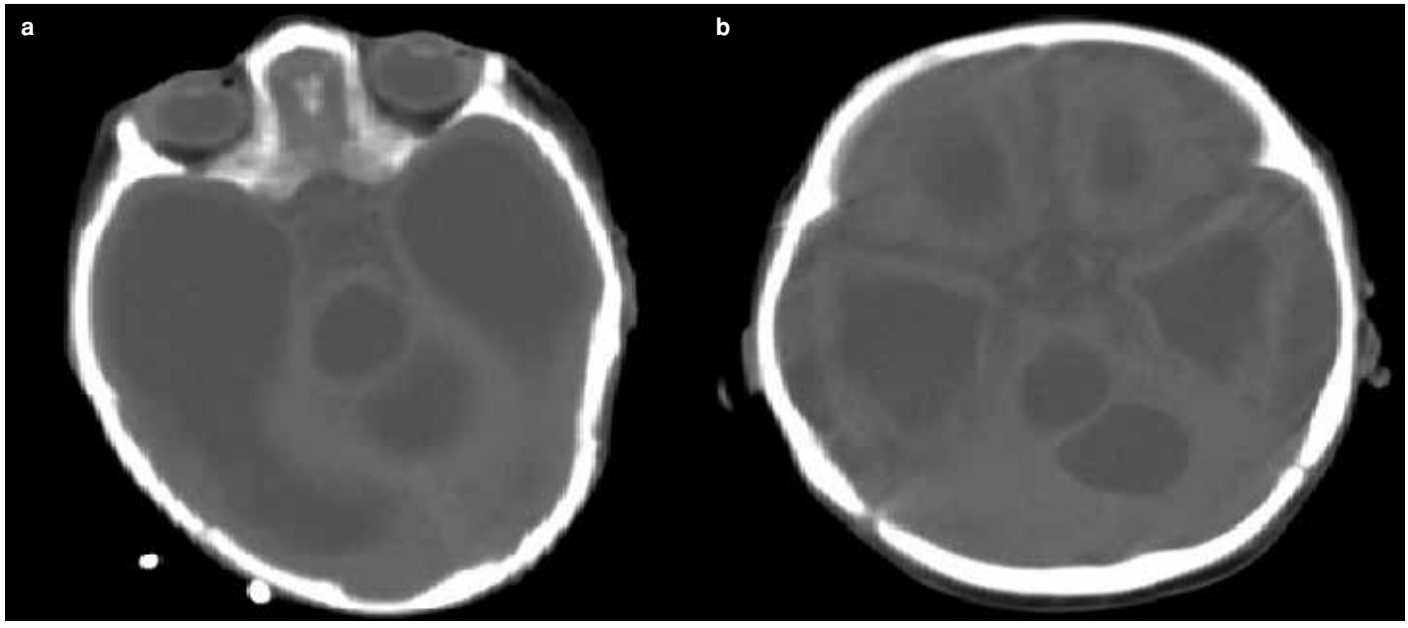

Figure 1. a, b. His imaging findings on admission; on admission, cranial CT showed tetraventricular hydrocephalus and hypodense cyst comprssing third and fourth ventricle minimally (a); and after treatment cranial CT showed decrease of hydrocephalus and cyst compared to cranial CT findings before the treatment (b)

There are no reports of the use of voriconazole for CNS candidiasis. Voriconazole achieves excellent levels in CSF (12). However, clinical experience with voriconazole for Candida CNS infections is limited. After flucytosine and liposomal amphotericin B as initial therapy, voriconazole seem to be appropriate as step down therapy for meningitis caused by *C. glabrata* or *C. krusei* (3). Whereas fluconazole plus caspofungin were administered in other hospital, liposomal amphotericin B was preferred as initial therapy in our hospital because the standard induction therapy for Candida meningitis is amphotericin B combined with or without flucytosine (3).

Despite treatment, *C. albicans* was isolated from CSF culture again. Subsequently, intraventricular liposomal amphotericin B was added to intravenous liposomal amphotericin B. Despite the fact that before the treatment MIC of amphotericin B was <1 mcg/mL for *C. albicans*, during the treatment MIC of amphotericin B increased to 2 mcg/mL for *C. albicans* that CSF culture yielded again. MICs were evaluated by the CLSI M27-A (The Clinical and Laboratory Standards Institute) macrodilution method. Currently, *C. albicans* is considered susceptible to amphotericin B at a concentration of 1 mg/L (MIC<1 mg/L) (13). The minimal drug concentration achieved at the infection site should be at least equal to the MIC for the infecting organism, and in vivo, the ratio between the maximum concentration of the drug and the MIC value is the best predictor for outcome (14).

Isolates with caspofungin and amphotericin B MICs of >1 mcg/mL and a fluconazole MIC of ≥64 mcg/mL were considered as resistant (15). Because of the MIC value resulted as 2 mcg/mL, the treatment was replaced by voriconazole plus flucytosine and then any microorganisms were not isolated from CSF culture again. The patient was successfully treated with a combination of voriconazole plus flucytosine for six weeks. After treatment V-P shunt was inserted and he was discharged from the hospital. To our knowledge voriconazole therapy was not reported in CNS candidiasis up to the present.

Conclusion

C. albicans isolates has rarely been resistant to amphotericin B. Antifungal susceptibility tests for *C. albicans* isolates should be repeated in patients that are not observed improvement with clinical and laboratory findings despite amphotericin B therapy. If MIC of amphotericin B is increased for *C. albicans* during treatment, rearrangement of treatment should keep in mind according to antifungal susceptibility.

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