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Clinical significance of *Candida* species isolated from cerebrospinal fluid

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Candida species have only rarely been isolated from the cerebrospinal fluid. Some of these isolates are true pathogens with a high morbidity and mortality, while others are only colonizers or contaminants. Spontaneous recovery from *Candida* meningitis has also been reported. The purpose of this study was to identify factors indicative of patients positive for *Candida* from cerebrospinal fluid who should receive antifungal therapy. A total of 36 patients with a positive cerebrospinal fluid culture for *Candida* were included in this retrospective analysis. Seventeen of these patients had received antifungal therapy under the impression of *Candida* meningitis. The differences in the case fatality rate and the duration of hospitalization between the antifungal treatment and untreated groups were statistically significant ($p<0.04$ and $p<0.005$, respectively). Statistical analysis showed a significant difference in the percentage of patients with previous ventricular shunt (14/17 vs 8/19, $p<0.05$), central venous line *in situ* (9/17 vs 1/19, $p<0.005$), multiple positive cerebrospinal fluid culture (11/17 vs 1/19, $p<0.0005$), isolation of *Candida* at least 20 days after hospitalization in adults (6/7 vs 1/13, $p<0.005$), and cerebrospinal fluid white blood cell count (median 77 vs 2 /mm^3, $p<0.005$). These results suggest that antifungal agent should be initiated promptly in patients whose cerebrospinal fluid is positive for *Candida* and who have one or more of the identified risk factors.

Key words: *Candida*, meningitis, risk factor

Candida species have become the fourth leading pathogen isolated from blood in the United States [1] and the leading pathogen of nosocomial bloodstream infection in a teaching hospital in Taiwan [2]. However, they have rarely been isolated from the cerebrospinal fluid (CSF). Many CSF isolates are true pathogens of *Candida* meningitis, which has a high morbidity and mortality if undiagnosed or treatment is delayed [3]. On the other hand, some isolates are just contaminants or colonizers, especially when the *Candida* is isolated from only a single CSF specimen or from specimens drawn through an indwelling central nervous system (CNS) device [4,5]. Moreover, cases of spontaneous recovery from *Candida* meningitis without receiving antifungal agent have also been reported [6,7]. Risk factors for *Candida* meningitis include premature infant [8], immunocompromised status [9-12], malignant disease (especially hematologic malignancy) [13,14], precedent or concomitant bacterial meningitis [5,7,15], neurosurgical procedure [5,7], intraabdominal surgery [3,16], use of broad-spectrum antibiotic [3,5,7,13], steroid [3,5,7,16], intravenous catheter [3], total parenteral nutrition [13], and parenteral drug abuse [17]. However, many of these risk factors have also been reported in association with candidal colonization [18-20]. This retrospective study aimed to identify factors that indicate whether patients with positive culture of CSF for *Candida* should be given antifungal agent, or whether they are likely to remain well without antifungal therapy.

Materials and Methods

Patients

The clinical microbiologic records of all positive fungal cultures at Taipei Veterans General Hospital from July 1987 through February 2001 were reviewed. Patients with *Candida* spp. isolated from CSF were included in this study. Patients were divided into 2 groups by whether they had received antifungal therapy or not. Data collected from medical records include demographic characteristics, underlying disease, clinical presentation, laboratory results, therapy, and outcome.

The body mass index (BMI; kg/m^2) of adults and weight of children was determined at the time of

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Candida isolation. Other information collected included duration of antibiotic therapy; steroid therapy and central venous line (CVL) *in situ* before candidal isolation; the interval from craniotomy (excluded those surgery for CNS device implantation); precedent bacterial meningitis; latest lumbar puncture; latest shunt implantation until isolation of *Candida*; the number of antibiotic classes; number of precedent shunt implantation procedures; and episodes of neutropenia prior to isolation of *Candida*. Fever was defined as an oral temperature higher than 38°C.

Microbiologic study and laboratory data

Cerebrospinal fluid was obtained via CNS device, lumbar puncture, or during craniotomy. The specimen for fungal culture was inoculated on brain-heart infusion agar and cornmeal agar with caffeic acid and incubated at 30°C. Yeast colonies were confirmed by microscopic examination with lactophenol cotton blue stain. Yeast underwent germ tube test for identification of *Candida albicans*. Those with negative germ tube test were identified by API-ATB 20C or 32C system (bioMèrieux Vitek, France).

Statistical analysis

Discrete variables were analyzed by chi-square test with Yates correction or Fisher's exact test, depending on the sample size; continuous variables are presented as median (range) and were analyzed by Mann-Whitney U test. Odds ratios with 95% confidence intervals were also calculated for the discrete variables. Statistical analysis was performed using SPSS (version 10.0; SPSS Inc, Chicago, IL, US) and Epi-Info (version 6.02). A p value less than 0.05 was considered significant.

Results

During the 14-year study period, there were 38 patients whose CSF specimens were positive for *Candida* spp. Among these patients, 36 with complete clinical and microbiologic records were included in the study. The *Candida* isolates were considered clinically significant in 17 patients who were treated with antifungal agents, with or without CNS device removal or replacement. The remaining 19 patients did not receive antifungal agents, while 6 of the 8 patients with indwelling CNS device had the device removed or replaced. In the antifungal treatment group, the mortality rate due to *Candida* meningitis was 23.5% (4/17 patients) and the median duration of hospitalization was 71 days (range, 29-957 days). In the untreated group, none of the patients died of *Candida* infection, and the median duration of hospitalization was 27 days (range, 5-110

Table 1. Comparison of underlying conditions in patients with and without antifungal treatment for *Candida* meningitis after positive CSF culture

Underlying condition	No. of cases (%)		OR (95% CI)	p
	Treated group n = 17	Untreated group n = 19		
Malignancy	5 (29)	3 (16)	2.22 (0.35-15.05)	NS
Neutropenia	3 (18)	1 (5)	3.86 (0.3-107-95)	NS
Head trauma	4 (24)	1 (5)	5.54 (0.47-46.81)	NS
DM	0	3 (16)		NS
Prior bacterial meningitis	7 (41)	4 (21)	2.63 (0.49-14.75)	NS
Concomitant bacterial meningitis	6 (35)	4 (21)	2.05 (0.37-11.67)	NS
Craniotomy[a]	4 (24)	4 (21)	0.86 (0.15-4.94)	NS
Intra-abdominal operation	3 (18)	2 (11)	1.82 (0.2-18.64)	NS
Precedent shunt	14 (82)	8 (42)	6.42 (1.13-41.23)	0.013
Previous lumbar puncture	7 (41)	5 (26)	1.96 (0.39-10.13)	NS
CVL *in situ*	9 (53)	1 (5)	20.25 (1.94-505.39)	0.001
Endotracheal tube in place	2 (12)	4 (21)	0.5 (0.05-4.00)	NS
Foley catheter in place	4 (24)	6 (32)	0.67 (0.12-3.64)	NS
Prior antibiotics usage	15 (88)	13 (68)	3.46 (0.48-30.34)	NS
Steroid therapy	9 (53)	9 (47)	1.25 (0.28-5.71)	NS
Concomitant TPN	4 (24)	2 (11)	2.62 (0.33-24.84)	NS
Concomitant amino acid infusion	3 (18)	2 (11)	1.82 (0.20-18.64)	NS
Chemotherapy	4 (24)	1 (5)	5.54 (0.47-146.81)	NS
Radiotherapy	2 (12)	0		NS

Abbreviations: OR = odds ratios; CI = confidence intervals; DM = diabetes mellitus; CVL = central venous line; TPN = total parenteral nutrition; NS = not significant.

[a]Excluded those with device implantation.

Table 2. Comparison of clinical features of patients with and without antifungal therapy after positive CSF culture for *Candida*

Clinical feature	No. of cases (%)		OR (95% CI)
	Treated group n = 17	Untreated group n = 19	
Fever	14 (82)	11 (58)	3.39 (0.59-21.39)
Consciousness deterioration	9 (53)	10 (53)	1.01 (0.22-4.60)
Device obstruction[a]	6/14 (43)	2/8 (25)	3.00 (0.35-30.52)
Seizure	5 (29)	2 (11)	3.54 (0.47-32.22)
Focal neurological sign	4 (24)	5 (26)	3.54 (0.47-32.22)
Headache	3 (18)	4 (21)	0.80 (0.11-5.45)
Meningeal sign	3 (18)	4 (21)	0.80 (0.11-5.45)
Shock	1 (6)	1 (5)	1.13 (0-45.66)

Abbreviations: OR = odds ratios; CI = confidence intervals
[a]Total number was 14 and 8 in treated and untreated group, respectively.

days). The fatality rate and duration of hospitalization were significantly greater in the antifungal therapy group ($p<0.04$ and <0.005, respectively).

There were 11 male and 6 female patients in the antifungal treatment and 11 male and 8 female patients in the untreated group. Patients of all ages were affected in both groups. However, most of the cases in the antifungal treatment group were children (10 children vs 7 adults), while adults predominated in the untreated group (6 children vs 13 adults). Thus, the median age was younger in the antifungal treatment group (3.7 vs 57 years, $p=0.146$). In both groups, all of the children affected were less than 10 years old. Comparison between the antifungal treatment group and the untreated group revealed that infants and neonates in the treatment group tended to be born prematurely (6/6 vs 1/3, $p=0.156$), while very low birth weight (VLBW; <1500 g) infants were found in equal percentage (3/6 vs 1/3). Nevertheless, neonates or infants with birth weight below 1 kg were found only in the treatment group (2 cases). The BMI of adults was lower in the antifungal treatment group (median [range], 20 [14.98-23.15] vs 22.6 [19.8-29.69] kg/m^2, $p=0.108$), but this difference was not significant. Notably, while 2 of the patients in the antifungal treatment group had BMI less than 19 kg/m^2, none in the untreated group had such a low BMI. In both groups, the body weight of about 70% children was below the 25th percentile of the comparative age (7/10 vs 4/6).

The underlying conditions of the 2 groups are compared in Table 1. Only prior CNS device implantation ($p<0.05$) and CVL *in situ* ($p<0.005$) were significantly different between the 2 groups. Among the patients in the antifungal treatment group, 14 had at least one (range, 1-13) CNS device implantation prior to disease onset. The median interval from the latest device implantation to candidal isolation was 61 days (range, 4-365 days). The CVL had been in place for a median of 11 days (range, 5-365) in 9 cases. Patients of both groups had been using the same classes of antibiotics prior to isolation of *Candida*, but antibiotics were used longer in the antifungal treatment group (median, 42 vs15 days, $p=0.053$). Otherwise, no significant difference was found in the duration or interval between other risk factors and *Candida* isolation. In both groups, most of the patients were

Table 3. Cerebrospinal fluid analysis and peripheral blood cell count of patients with and without antifungal therapy after positive CSF culture for Candida

	Median (range)		*p*
	Treated group	Untreated group	
CSF analysis			
WBC (/mm^3)	77 (0-3820)	2 (0-335)	0.003
Protein (mg/dL)	116 (24-2800)	69 (10-600)	NS
CSF/serum glucose level (%)	0.41 (0.26-1)	0.65 (0.13-1)	0.052
Peripheral hemogram			
WBC (/mm^3)	17 200 (300-61 000)	12 700 (1100-24 100)	NS
Hb (g/dL)	11.4 (9-15.4)	11.5 (7.9-16.5)	NS
Platelet (/mm^3)	214 000	259 500	NS

Abbreviations: CSF = cerebrospinal fluid; WBC = white blood cell; Hb = hemoglobin; NS = not significant

Table 4. Mycological studies of the 36 patients with and without antifungal therapy after positive CSF culture for *Candida*

Clinical feature	No. of cases (%)		OR (95% CI)	*p*
	Treated group n = 17	Untreated group n = 19		
Precedent candidal isolation	6 (35)[a]	3 (16)[b]	2.91 (0.48-19.14)	NS
Concomitant isolation from other side	4 (24)[c]	1 (5)[d]	5.54 (0.47-146.81)	NS
Multiple isolation from CSF (≥2 set)	11 (65)	1 (5)	33.00 (3.06-845.82)	<0.0001
Isolation from CSF 20 days after admission in adult[e]	6/7 (86)	1/13 (8)	72.00 (2.72-11291.84)	0.00118
Candida from lumbar puncture	5 (29)	12 (63)	0.21 (0.04-1.07)	NS
Candida from CNS device	12 (71)	6 (32)	5.20 (1.03-28.52)	0.045
Candida from craniotomy	0	1 (5)		NS

Abbreviations: OR = odds ratios; CI = confidence intervals; CSF = cerebrospinal fluid; CNS = central nervous system; NS = not significant
[a]Three from CSF, one from pus of craniotomy wound, one from urine, one from oral cavity, skin (by pathology), and urine subsequently.
[b]Two from urine, one from sputum.
[c]Two from blood, one from urine, one from blood and urine.
[d]From urine.
[e]The number of adult patients were 7 and 13 in the treatment and non-treatment group, respectively.

symptomatic during candidal isolation (Table 2). No distinctive clinical features associated with initiating antifungal therapy were identified.

Analysis of continuous variables for differences in CSF parameters (Table 3) showed significant difference in CSF white blood cell (WBC) between the antifungal treatment and untreated groups (median, 77 vs 2 /mm^3, $p<0.05$), especially when using a value of >40 /mm^3 as a cut point ($p<0.005$). In patients with pleocytosis (CSF WBC >5 /mm^3), neutrophil predominance was found equally in both groups (7/12 vs 4/6, $p= 0.86$). The ratio of CSF/serum glucose was lower (0.41 vs 0.65, $p=0.052$), but protein level was higher in the antifungal treatment group (116 vs 69 mg/dL, $p=0.117$), with the difference in CSF/serum glucose ratio nearly approaching significance. The blood cell count (Table 3) and isolated *Candida* species were comparable in the 2 groups. *C. albicans* was the most common isolate, comprising for 11 of 17 and 9 of 19 isolates in the 2 groups, followed by *Candida parapsilosis* (2 and 3), *Candida glabrata* (2 and 2), and *Candida tropicalis* (2 and 1). The species of 3 isolates was not determined in the untreated group. In other mycological study, the number of patients with multiple (≥2 sets) positive CSF cultures were significantly different between the 2 groups (11/17 vs 1/19, $p<0.0005$). Age was not associated with the timing of *Candida* isolation. However, in adult patients, most of the *Candida* was isolated at least 20 days after hospitalization in the antifungal treatment group (6/7 vs 1/13, $p<0.005$). Prior *Candida* isolation was noted in 6 and 3 cases in the 2 groups, respectively ($p=0.3351$). However, only 3 patients in the antifungal treatment group had prior isolation of *Candida* from a CSF sample obtained during implantation of a CNS device, and this difference approached significance ($p=0.09$). Gram stain was positive in 3 (18%) patients with antifungal treatment, but gram stain was not done in all specimens, which made comparison of the 2 groups impractical.

Discussion

Many risk factors have been reported in association with *Candida* meningitis. McCullers *et al* [13] reported the first case-control study between children with *Candida* meningitis and children with comparatively immunosuppressed status. They found that duration of fever, antibiotics therapy, profound neutropenia, and use of total parenteral nutrition were associated with acquisition of this disease in univariate analysis, but only the latter 2 factors approached significance in the multivariate analysis. However, there have been few studies of the clinical significance of *Candida* isolates from CSF [4,5].

Although the case number in this study is limited, this is the largest reported comparative study of the clinical significance of CSF isolation. Buch and Pfister's review [6] of 80 cases of *Candida* meningitis found a slight male predominance (male/female ratio, 1.5:1). The sex ratio was identical in both groups. *Candida* meningitis has been reported in every age group [3,5,6]. This study found that patients who received antifungal therapy were younger. This finding is compatible with the results of Buch [21] that there has been a gradual shift in the demographics of *Candida* meningitis from adults to infants since 1958. Among neonates and infants, prematurity and VLBW have been implicated as risk factors for *Candida* meningitis [4]. In this study, infants and neonates who received antifungal therapy

tended to be born prematurely, but the significance of this difference could not be assessed because of the small sample size. Treatment with antifungal agents should be considered whenever *Candida* is isolated from the CSF in children. This is especially important in premature infants with VLBW [4], as reported mortality and neurodevelopmental disability rates were high [22]. In adult patients in this study, those who received antifungal therapy had a lower median BMI. As BMI is a good index of nutritional status [23], it is not surprising that patients with malnutrition have impaired cellular immunity associated with high risk for invasive candidal infection [24]. When *Candida* is isolated from CSF in adults with a low BMI, especially when lower than 19 kg/m^2, antifungal agents may be considered. However, determination of specific indications requires further large prospective studies.

Although malignancy did not reach significance as a differentiating factor in this report, treatment with an antifungal agent should be considered whenever *Candida* is isolated from CSF in patients with malignancy because of the high mortality in these patients, even during antifungal therapy [13]. Central venous line and precedent shunt implantation were 2 important factors associated with antifungal treatment and are well-known risk factors for CNS candidiasis [3,5,25]. *Candida* may be inoculated into the bloodstream and CNS via damaged skin by these 2 procedures. In addition, the duration of antibiotics therapy was associated with the acquisition of *Candida* meningitis in a previous study [13], and it also approached significance in this study (p=0.053). Geer and Gordon's study [5] of the postneurosurgical population found that several signs had a significant difference in frequency between patients treated with antifungal agent and those without, including meningismus, focal neurologic sign, and altered mental status. However, none of these clinical presentations was prevalent in either group in this study. In this study, the untreated group included also non-neurosurgery patients, who had severe underlying disease that may have contributed to their risk of *Candida* infection. This may be one of the reasons for the similar clinical presentation in the 2 groups. Chiou *et al* [25] suggested that repeated obstruction in a patient with CSF shunt should raise suspicious of infection; however, there was no difference of this presentation in this study.

Pleocytosis was usually present in patients with *Candida* meningitis. Although a few studies showed no significant difference in pleocytosis between patients with and without antifungal treatment, patients with antifungal treatment in this study had a significantly higher CSF WBC count. Treatment with an antifungal agent should be considered in patients whose CSF WBC is over 40 $/mm^3$. In the antifungal treatment group, the CSF/serum glucose ratio was lower than, and the protein level was higher than, that in the untreated group, but this difference did not reach significance. Almost all common *Candida* species have been reported as pathogens for meningitis, with *C. albicans* being the most common [3,5]. This study did not show predominance of any species in either group. This finding suggests that the clinical significance of *Candida* isolate is not based solely on the species. Previous studies have reported that colonization was an important preceding factor for infection [13]. Previous isolation of *Candida* was noted in 6/17 versus 3/19 cases in the 2 groups (p=0.3351). However, only 3 children in the antifungal treatment group had previous *Candida* isolation from CSF. These isolates were initially considered to have been due to contamination, but antifungal therapy was initiated after repeated positive isolation from CSF and clinical features suggestive of meningitis. Indeed, repeated positive CSF *Candida* culture has been implicated as the single most important indicator for the initiation of therapy for fungal meningitis [4,5]. When *Candida* is positive only in a single CSF culture, therapy may be considered in non-neurosurgical patients [5], high-risk infants [8], immunocompromised hosts, patients with neurological signs, or patients with CSF parameters compatible with meningitis and associated risk factors simultaneously [4]. Nevertheless, in patients without an associated risk factor and abnormal CSF parameters, repeated CSF culture is recommended before *Candida* isolates are discarded as colonizers or contaminants [5], as mortality rates reach 61% among *Candida* meningitis patients receiving no specific antifungal agent [6]. *Candida* meningitis usually occurs nosocomially [7,16]. Parker *et al* [27] found that patients with deep candidiasis who had CNS involvement tended to be hospitalized for more than 20 days compared with those without (74% vs 59%). In this study, no relationship was found between age and the interval between the day of admission and the day of collection of a positive specimen from CSF. However, when *Candida* was isolated from CSF 20 days after hospitalization in an adult patient, it was very likely (6/7) to be a true pathogen. This finding deserves further larger prospective studies before a definite conclusion can be reached, as this study, with its small sample size, is the first to report this correlation. The significance of *Candida* isolated from CSF through shunt was controversial [25]. Nevertheless, 12 of the 18 patients in this study with this condition received treatment and

2 of them died of *Candida* meningitis. Accordingly, any positive *Candida* culture from CSF sampling from a CNS device should be considered individually.

In summary, patients whose CSF is positive for *Candida* should receive antifungal agent when they have any of the following risk factors: prior CNS device implantation; CVL *in situ* for a long duration; high value of CSF WBC (>40 /mm^3); multiple *Candida* isolation from CSF; and isolation of *Candida* from CSF after 20 days of hospitalization in adults. Due to high mortality of *Candida* meningitis in cases of delayed or inadequate treatment, any positive *Candida* culture from CSF specimens should be considered seriously before being classified as contaminants and colonizers. Repeated culture and further surveillance are advised.

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