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ORIGINAL ARTICLE

Clinical and microbiological characteristics of *Candida* meningitis/ventriculitis in children

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Abstract

Background: *Candida* meningitis/ventriculitis is rather rare during childhood. In this study, we investigated the clinical characteristics, risk factors, treatment, and prognosis of patients with *Candida* meningitis/ventriculitis.

Methods: Patients under the age of 18 years who were diagnosed with *Candida* meningitis/ventriculitis were evaluated retrospectively.

Results: A total of 10 cases with *Candida* meningitis/ventriculitis were analyzed. Three patients (30%) were below the age of one, and two (20%) were neonates. The two most common underlying conditions were hydrocephalus shunt and prematurity. Predisposing factors were a history of broad-spectrum antibiotic use, external ventricular drainage, total parenteral nutrition, central venous catheter, and staying in intensive care. The cerebrospinal fluid culture was positive in all patients, and 10% (1/1) had bacteremia. Of the isolates, 50% were *C. albicans*, 30% were *C. tropicalis*, 10% were *C. lusitaniae*, and 10% were *C. dubliniensis*. Fluconazole treatment was initiated in four (40%) and voriconazole in three (30%) patients. Two patients received combined treatment (amphotericin B + fluconazole/voriconazole). The median treatment duration was 38.6 days (range: 16–70 days). Three patients received intraventricular Amphotericin *B.Central* nervous system devices which were assumed to be infected were removed. A complication of endophthalmitis developed in one patient. The mortality rate was 10%.

Conclusions: Among agents causing meningitis/ventriculitis, *Candida* should also be kept in mind in premature neonates and patients with ventricular-peritoneal shunts. The history of antibiotic use and external ventricular drainage are important predisposing factors. It can be successfully treated with fluconazole, voriconazole, amphotericin B, and removal of the central nervous system device.

Keywords: *Candida*, Ventriculitis, Meningitis, Treatment, Children.

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INTRODUCTION

Central nervous system (CNS) involvement is very rare among invasive *Candida* infections in children. *Candida* species occupy the most common meninges within the CNS (1). *Candida* species usually cause acute meningitis during dissemination (2). In addition to hematogenous spread, they can reach the brain with craniotomy and ventriculoperitoneal shunt or other CNS devices (1). And they cause serious mortality and morbidity (3). *Candida* meningitis (CM) is most commonly seen in newborns with candidemia (2). 5%-9% of newborns with candidemia are accompanied by meningitis (4). Very low birth weight premature (PM) infants are a significant risk group for CM (5). Although CM is seen in healthy people, people with weak immune systems are also at risk (5). Previous antibiotic and steroid use, a central venous catheter (CVC), recent neurosurgery/ Cerebrospinal fluid (CSF) drainage system, abdominal surgery, and intravenous drug use have been reported as risk factors for CM (3, 6). Generally, the clinical symptoms are like acute bacterial meningitis, however, it can rarely cause chronic meningitis symptoms (1). Furthermore, hematogenous spread and symptoms related to eye, skin, and endocardial involvement can also be seen. There are limited information in the literature on CM in children.

In this study, we investigated the demographic, clinical characteristics, risk factors, treatment, and prognosis of patients diagnosed with *Candida* meningitis.

MATERIALS AND METHODS

Patients under the age of 18 and diagnosed with *Candida* meningitis followed between January 2015 and December 2021 were included in the study. Patients with *Candida* species grown in the CSF culture were obtained from microbiology laboratory records. The diagnosis of *Candida* ventriculitis/meningitis (CVM) was determined as patients with bacterial meningitis symptoms and signs according to age group, and as patients who had pleocytosis, low glucose, high protein in CSF analysis, and *Candida* growth in CSF culture. Patients without risk factors for CNS infection, without signs and symptoms of CNS infection, and without CSF glucose, protein, and normal pleocytosis were excluded from the study.

Demographic characteristics of the patients, predisposing factors, clinical management, CSF examination results, details of antifungal treatment, antifungal sensitivity results, culture results, echocardiography, and eye examination results were analyzed and recorded in the leaflets. CSF was obtained by lumbar puncture or CNS devices (lumbar drainage, external ventricular drainage [EVD], or shunt pump). For *Candida* identification and antifungal susceptibility tests, MIC values against amphotericin B, caspofungin, micafungin, fluconazole, flucytosine, and voriconazole were determined using the VITEK 2 Compact® (bioMeriéux, France) system and identification cards (YST) and antifungal susceptibility cards (AST-YST01).

With improvement of clinical symptoms and signs, normalization of CSF glucose, protein, pleocytosis, and absence of culture growth, patients who resolved completely on MRI in the presence of cerebral abscess were considered cured. The duration of treatment was decided according to the improvements. In addition to intravenous therapy, the infected intraventricular device was removed. Intrathecal (IT) treatment was not routinely applied. Intrathecal therapy was applied to the patients who did not improve despite appropriate antifungal treatment, whose CSF findings did not regress, and whose CSF culture growth continued. We administered amphotericin B deoxycholate through the device into the ventricle at a dose of 0.01 to 0.5 mg in 2 mL 5% dextrose in water (7, 8). Because of the lack of clear information about the IT duration, the decision was made on a patient basis. It was discontinued in patients with improved pleocytosis and sterile CSF.

In patients diagnosed with CM, the death that occurred within 30 days after *Candida* growth in CSF/Blood culture was determined as death ascribed to *Candida*.

Our study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from Çukurova University Non-Interventional Clinical Research Ethics Committee (Date: 03/06/2022, Decision No:123).

Statistical Analysis

For statistical analyzes, SPSS version 23.0 was employed. Continuous measurements were summarized as means, deviation, and minimum-maximum, whereas categorical measurements were presented as numbers and percentages.

RESULTS

A total of 10 cases with CVM were analyzed. The median age was 41.3 months, (range: 2–180 months). Three patients were under the age of one, and two (20%) were premature infants. Seven (70%) patients were female. The most prevalent symptoms were vomiting, fever, proneness to sleep, and headache (50%, 30%, 20%, and 20%, respectively).

All patients had an underlying condition, and the two most common underlying conditions were hydrocephalus shunt and prematurity. Of the CVM, 60% (6/10) were associated with hydrocephalus shunt, where the postoperative, and spontaneous meningitis/ventriculitis manifestations accounted for 20% (2/10), and 20%(2/10) cases, respectively. Patient demographics, clinical characteristics, treatment, and prognoses are summarized in Table 1.

Table 1. Patient demographics, clinical characteristics, treatment and prognosis

Case	Age (Months) /Sex	Application Complaint	Underlying Disease	Risk Factors	Species / Repeat Number	CSF Analysis	PCT/ CRP	Tx and Duration	Additional Tx	Prognosis
1	20 / M	Vomiting , Proneness to sleep	H, V-P shunt	-	*C. tropicalis*/3	Glu:0 P:1316 Diffuse WBC	0.4/297	AmB(20) + FLU (13), after VCZ (20)	Shunt removal	Cure
2 **	2/F	Deterioration in general condition	PM (27 weeks)	Antibiotic use, Admission to intensive care unit CVC, TPN	*C. albicans*/5	Glu:1 P:234 60/mm^3 WBC	0.08/-	AmB (30) + FLU (39), after AmB(20) + VCZ (20)	IT AmB (14 day)	Cure
3	40/F	Fever	H, V-P shunt	EVD, Antibiotic use,	*C. tropicalis*/2	Glu:42 (SG:80) P:196 20/mm^3 WBC	0.08/3	VCZ(21)	EVD replacement	Cure
4	26/M	Fever, Vomiting , Clouding of consciousness	OBT, V-P shunt	EVD, Antibiotic use, CVC, TPN Admission to intensive care unit, History of surgical operation	*C. albicans*/9	Glu:11 (SG:127) P:193 70/mm^3 WBC	0.06/8	FLU(33)	EVD replacement + IT AmB (10day)	Cure
5*	5/F	Vomiting	H, V-P shunt	EVD, Antibiotic use, CVC	*C. lusitaniae*/3	Glu:82 (SG:90) P:420 330/mm^3 WBC	0.06/7	VCZ(49)	EVD replacement	Cure
6	14/F	Fever	H, V-P shunt	EVD Antibiotic use	*C. albicans*/2	Glu:4 (SG:81) P:417 120/mm^3 WBC	0.04/14	FLU(38) FLU(32)	EVD replacement	Cure
7	180/F	Headache , Proneness to sleep	H, V-P shunt	EVD, Antibiotic use,	*C. albicans*/3	Glu:76 (SG:108) P:420 Diffuse WBC	0.2/228	VCZ (24)	EVD replacement	Cure
8	72/E	Headach, Vomiting	OBT, V-P shunt	Antibiotic use, Admission to intensive care unit, History of surgical operation, Steroid use	*C. albicans*/1	Glu:51 (SG:192) P:1100 350/mm^3 WBC	0.01/12	AmB(32) after VCZ (16)	Shunt removal + IT AmB (12 day)	Died
9	2/F	Vomiting , Apnea	PM (30 weeks)	Antibiotic use, Admission to intensive care unit, TPN	*C .tropicalis*/1	Glu:46 (SG:192) P:95 0/mm^3 WBC	0.8/6	FLU (16)	-	Cure
10	52/M	Convulsion	H, V-P shunt	Antibiotic use	C. *dubliniensis*/1	Glu:9 (SG:89) P:3100 30/mm^3 WBC	0.06/4	FLU (42)	Shunt removal, Abscess drainage	Cure

*Concurrent blood culture has growth

**Case with endophthalmitis

F: Female, M: Male, H: Hydrocephalus, PM: Premature, V-P: Ventriculoperitoneal, OBT: Operated Brain Tumor, TPN: Total Parenteral Nutrition, CVC: Central Venous Catheter, EVD: External Ventricular Drainage, Tx: Treatment. IV: Intraventricular, Glu: Glucose (mg/dl), SG: Serum Glucose (mg/dl), P: Protein (mg/dl), WBC: White Blood Cell, PCT: Procalcitonin (Normal range: 0-0.5 ng/ml), CRP: C-Reactive Protein (Normal range: 0-8 mg/L), AmB: Amphotericin B, FLU: Fluconazole, VCZ: Voriconazole, IT: Intrathecal , CSF: Cerebrospinal Fluid.

The most common infections associated with CNS devices, which were a risk factor, were due to EVD, followed by ventriculoperitoneal shunt. Two patients with spontaneous meningitis were premature infants. Predisposing factors, nine patients had a history of broad-spectrum antibiotic use. Subsequently, EVD, total parenteral nutrition (TPN), a long stay in intensive care, and CVC, were the most prevalent predisposing factors (Table 1).

In hospital-acquired cases, culture growth was observed after a median of 30.1 days (range: 5–82 days) of hospitalization. The most common CSF abnormalities were pleocytosis in eight (80%) cases, elevated protein concentrations in 100%, and hypoglycorrhachia in seven (70%). CSF culture was positive in all patients, and 10% (1/1) had bacteremia (Case 5). Of the isolates, 50% were *C. albicans*, 30% were *C. tropicalis*, 10% were *C. lusitaniae*, and 10% were C. *dubliniensis*. Complications other than endophthalmitis were detected in only one patient

Case 2 was 27 weeks premature and on the 58th day of neonatal intensive care unit admission, CSF taken due to deterioration in his general condition was compatible with meningitis and C. albicans grew in his culture. Endophthalmitis was detected in the general scan. Amphotericin B and fluconazole-combined treatment was started (Since there is no flucytosine in our country). As growth continued in CSF cultures, external ventricular drainage was inserted and IT amphotericin B was added to the treatment. Treatment because CSF findings did not regress and C. albicans growth was 5 times. Amphotericin B and voriconazole were switched. *Candida* meningitis was healed after 59 days of treatment.

Case 6 was hospitalized with a ventriculoperitoneal shunt infection. The shunt was removed. Fever occurred again on the 19th day of EVD and systemic antibiotic therapy. *C. albican*s grew in CSF culture. Fluconazole was started. It improved after 38 days of treatment. 13 days after the antifungal was discontinued, growth occurred again in the CSF culture. Fluconazole was started again and completely recovered after 32 days of treatment.

No resistance was detected against amphotericin B (AmB), caspofungin, mycofungin, fluconazole (FLU), flucytosine (5- FC) and voriconazole (VCZ) in any patient.80% of the patients received single antifungal therapy. Of the patients who received single antifungal therapy, four of them received FLU, and three they received VCZ. One patient was initially started on AmB therapy. VCZ treatment was started due to resistant hypopotassemia (Case 8). One patient was treated with AmB and FLU combined, however, due to continued growth, a single VCZ treatment was started (Case 1).

The median treatment duration was 38.6 days (range: 16–70 days). In addition to systemic therapy, three (30%) patients received IT AmB treatment (Cases 2, 4, 8). IT AmB was added due to recurrent growth in CSF culture in cases 2,4, and IT AmB was added in case 8 due to continued pleocytosis. IT treatment was discontinued when CSF became sterile, and pleocytosis regressed. The duration of treatment applied was between 10 and 14 days.

The infected CNS devices were removed from the patients with CVM (8/8) (V-P shunt was removed in 2 patients, EVD was changed in 6 patients). Abscess drainage was performed in one patient (Case 10). The mortality rate was 10% (Case 8).

DISCUSSION

Fungal infections of the central nervous system are rare and life-threatening serious infections. *Candida* is the most common cause of CNS fungal meningitis. In a study conducted on children, they reported that 94.5% fungi isolated in CSF were *Candida* isolates (9). However, it may cause an isolated intracranial abscess or may be associated with meningitis (1, 10). In our study, we detected ventriculitis/abscess in only one patient. Premature neonates are at risk of CM and systemic candidemia. *Candida* often causes CM in the presence of other CNS devices, hematogenous or craniotomy, and V-P shunt, during disseminated candidiasis in premature neonates. As a complication of neurosurgical procedures, CM is an important cause of mortality and morbidity in neonates. Among the invasive *Candida* infections of neonates, CM was detected at a rate of 22% and their mean age was reported to be 26.2 weeks (11). Only two of our patients were premature neonates. Although no accompanying candidemia was detected, one patient had hydrocephalus due to intracranial bleeding and 27-week-old invasive *Candida* risk factors (Case 2).

Most cases of CM occur in patients with neurosurgery and CNS devices (lumbar drainage, external ventricular drainage, VP shunt). In a study conducted in the literature, it was reported that 71.4% (30/42) of those with *Candida* growth in their CSF were neurosurgery patients (12). 80% of our patients had a CNS device. While most of them were V-P shunt patients, only two patients had EVD inserted after brain tumor surgery. Fungal infection should be kept in mind when meningitis/ventriculitis develops in pediatric patients who have a CNS device inserted for any reason. In cases where there is no response to antimicrobial treatment, even if there is no culture growth, a treatment plan in this direction can be life-saving. Apart from PM and CNS devices, important risk factors are known as prolonged antibiotic use, CVC, TPN, immunosuppressant corticosteroid use, chemotherapy, recent neurosurgery or intra-abdominal surgery, and intravenous drug abuse (3, 6). Most of our patients (9/10) were also using antibiotics before. Only one patient had used steroids due to cerebral edema (Case 8). We did not any patients receiving immunosuppressive or KT. Although the possibility of invasive fungal infection is high in immunosuppressive patients, the two most common and most important risk factors in CM are the use of antibiotics, addition to brain surgery or CNS device.

It has been reported that *C. albicans* is mostly isolated in patients diagnosed with CM (6, 11). Although *C. albicans* is a very common species, there has been an increase in non-albicans *Candida* species recently. In our study, *C. albicans* was isolated in half of the patients and *C. tropicalis* was isolated in 30% of our patients. Lijun Xu et al. reported that they isolated 28.6% *C. albicans* and 35.7% *C. parapsilosis* in their study and reported results supporting that non-albicans *Candida* species were more common (12). In a study consisting only of pediatric patients with cancer, it was reported that they isolated *C. tropicalis* in all patients (13). Chen et al. reported that they detected *C. albicans* in half of their patients (14). In the literature, *C. famata, C. tropicalis, C. glabrata, C. dubliniensis, C. lusitaniae* and *C. util* can cause non-albicans *Candida* (11, 12, 14–16). Meningitis caused by *C. duplinienis* has been reported in adult cases, but no pediatric cases have been reported before. We had one case of *C. lusitaniae* and one case of *C. dubliniensis that* we isolated. These results suggest that there will be an important problem in rare fungi together with non-albicans *Candida* in the future.

For treating CM, liposomal AmB alone or along with oral 5-FC is recommended (7). If the patient is sensitive, FLU is also recommended. AmBdeoxycholate is recommended for initial treatment in the neonatal period. Baratgar et al. reported that they successfully treated six patients under the age of six months, with V-P shunt infection due to *Candida* with AmB (17). Fernandez et al. started AmB in all the 23 neonates with CM, and they combined five patients' treatments with 5-FC (11). They reported that at the beginning of treatment in adult patients with CM, they used FLU and VCZ, and they also switched to VCZ while using FLU (12). In our study, we initiated most of the patients with FLU or VCZ because of good CSF transmission. We treated two patients with a combination of AmB and FLU/VCZ antibiotics. Since there is no 5-FC in our country, we could not use it in treatment. The treatment period of CNS *Candida* infections can last from weeks to months and this period varies from patient to patient. In the case series presented by Chen et al., they reported a case in which they gave treatment for as long as 23 weeks (18). In our study, we had a case that we treated for up to 70 days. Although intraventricular therapy is not routinely recommended, intravenous therapy may be inadequate from time to time in patients with CNS drainage such as V-P shunt. Cases in which successful results were obtained with the application of intraventricular AmB have been reported in the literature (19, 20). We successfully treated three of our patients by administering intrathecal AmB. CNS devices that are assumed to be a source of and colonized with *Candida* should be removed, this has great importance in the success of treatment. In our study, we either changed all the CNS devices or removed them from all patients.

The prognosis of *Candida* meningitis may vary according to many factors such as age, underlying disease, antifungal drug resistance, and time of diagnosis. In a study on patients under six months of age in the literature, a mortality rate of 0% was stated (17). It has been reported that six of the 23 patients with CM in the neonate period were expired (11). Lijun Xu et al. reported 50% mortality in their CM cases (12). In a study conducted on patients other than neonates, 42% of CM-related deaths were reported (21). Chen et al. detected a mortality rate of 11.1% in neurosurgery patients (14). In our study, the mortality rate was 10%. Mortality rates differ in studies reported in the

literature. We believe that keeping CM in mind in patients who are in the risk group, and who do not respond to antibiotic treatment and initiating antifungal therapy early on will reduce prognosis and mortality.

In conclusion, *Candida species* are rare agents in the etiology of meningitis/ventricülitis in childhood. The clinic is nonspecific. It is a more common species in premature neonates and patients who have undergone neurosurgery and have a CNS device. Long-term use of antibiotics is the most important predisposing factor. Most patients can recover with systemic FLU, VCZ, AmB, and intraventricular AmB and the removal of CNS devices.

Decleration

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

Our study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from Çukurova University Non-Interventional Clinical Research Ethics Committee (Date: 03/06/2022, Number of Meeting/Decision No:123).

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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