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ORIGINAL ARTICLE

Ten-year experience of rhinocerebral zygomycosis in a teaching hospital in Tehran

Mitra Barati[1*], Mahshid Talebi-Taher[1], Marzieh Nojomi[2], Fatemeh Kerami[1]
[1] *Pediatric Infectious Diseases Research Center, Iran University of Medical Sciences, Tehran, Iran*
[2]*Department of Community Medicine, Iran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Background: Rhinocerebral zygomycosis is a rare, rapidly progressive and often fatal fungal infection occurring in several immunocompromised states. Prior investigators have reported an increasing incidence among Iranian population; therefore, we decided to present the clinical features and treatment outcome of a group of patients with rhinocerebral zygomycosis.

Patients and methods: Medical records of all cases with the diagnosis of rhinocerebral zygomycosis attending Rasoul-e-Akram Hospital, Tehran, Iran, were retrospectively reviewed from 1997 to 2007. Age, gender, predisposing illness, surgical procedures, and treatment outcomes were reviewed.

Results: Totally, 30 patients (17 males and 13 females) were reviewed with a mean age of 49.4±20.3 years. The lag time between onset of symptoms referable to zygomycosis and commencement of amphotericin B was 1 to 90 days with median of 10 days. An association between delayed treatment and mortality was found (p=0.01). Visual loss was observed in 53.3%. The ethmoid (86.6%) and maxillary sinuses (66.6%) were most commonly involved. Eighteen patients had underlying diabetes mellitus (60%). All patients received medical treatment, while 28 (93.3%) underwent surgical intervention. Twenty three patients (76.7%) had orbital involvement with a mortality rate of 43.5%. The overall mortality rate was 40% (12 cases). Patients with higher doses of amphotericin B and multiple surgical intervention had lower mortality rate (p=0.00 and p=0.01, respectively). Factors such as age, gender, predisposing diseases, orbital involvement, multi-sinus involvement, and white blood cell count had no impact on survival rate.

Conclusion: Institution of aggressive surgical debridement of devitalized tissue and the timely initiation of systemic medical therapy is critical for good outcome.

Keywords: *Rhinocerebral zygomycosis, Treatment, Prognosis, Diabetes mellitus*.
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INTRODUCTION

Rhinocerebral zygomycosis is a serious and uncommon invasive and often fatal fungal infection occurring in several immunocompromised states including diabetes, which is the most common (up to 70%) predisposing factor (1). The disease originates in the nasal/sinus mucosa after inhalation of fungal spores and takes a rapidly progressive course extending to neighboring tissues, including orbit and sometimes to brain (2,3). Zygomycosis causes a very high residual morbidity and mortality due to the angioinvasive property of the fungus, thereby causing vascular occlusion and consequently resulting in extensive tissue necrosis

Received: 3 January 2010 *Accepted*: 4 July 2010
Reprint or Correspondence: Mitra Barati, MD.
Pediatric Infectious Diseases Research Center, Iran University of Medical Sciences, Tehran, Iran.
E-mail: mitra_baraty@yahoo.com

(4-6). Impaired delivery of antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in these patients.

The incidence of rhinocerebral zygomycosis has been increased during the recent decades (2,4,6), hence, we decided to present the clinical features and treatment outcome of a group of Iranian patients with rhinocerebral zygomycosis attending our hospital during a 10-year period.

PATIENTS and METHODS

Medical records of all cases with the diagnosis of rhinocerebral zygomycosis attending Rasoul-e-Akram Hospital, Tehran, Iran, were retrospectively reviewed from 1997 to 2007. Only histologically confirmed cases were included. This was primarily determined by the tissue morphology with using periodic acid Schiff and gomori's methenamine silver staining (non septate, thick-walled hyphea with right-angle branching). Age, gender, predisposing illness, surgical procedures, and treatment outcomes were reviewed.

Data were analyzed using SPSS software (version 11.5, SPSS Inc., USA) and the association between risk factors and poor survival rate were analyzed by chi square and t-test, when appropriate.

RESULTS

The study population included 17 males and 13 females with the mean (± standard deviation) age of 49.4±20.3 years. Totally, 18 patients had underlying diabetes mellitus (60%), of whom 4 had type 1 diabetes mellitus. Of 14 patients with type 2 diabetes mellitus, 4 were on insulin and 10 on oral hypoglycemic drugs. The mean duration of diabetes was 6.7±6.6 years (a range, 0-20 years). The mean blood glucose level was 227±56 mg/dl (a range, 150-400 mg/dl) among diabetics at admission. Two patients had diabetic ketoacidosis, but none presented with hyperosmolar hyperglycemic state. Other associated diseases were hematologic malignancy in 7 patients (23.3%), neutropenia in one (3.3%), glucocorticosteroid use in two (6.7%), and only one patient (3.3%) had no identified predisposing illness. Among dead subjects, 5 had diabetes mellitus (41.6%) and 7 had other underlying diseases (58.3%) (p=0.13). Clinical features of patients are summarized in table 1.

Table 1. Characteristics of patients with rhinocerebral zygomycosis

Characteristic	Number (%)
Age (yrs)	49.4±20.3
Gender	
Male	17(56.7)
Female	13(43.3)
Underlying condition	
Diabetes mellitus	18(60)
Hematological malignancy	7(23.3)
Neutropenia	1(3.3)
Glucocorticosteroid usage	2(6.7)
Rhabdomyosarcoma	1(3.3)
No underlying illness	1(3.3)
Presenting symptoms	
Fever	6(20)
Headache	10(33.3)
Vomiting	4(13.3)
Visual loss	16(53.3)
Orbital involvement	23(76.7)
Palatal necrosis	8(26.7)
Eye redness	17(56.7)
WBC (/mm^3)	8298±5512
Paranasal sinus involvement	29(96.7)
One sinus	10(33.3)
Two sinuses	14(46.7)
Three sinuses	4(13)
Four sinuses	1(3.3)
Treatment	
Medical	2(6.7)
Surgical and medical	28(93.3)
Mortality	12(40)

On plain radiography and computed tomography imaging, almost all patients (96.7%) had evidence of paranasal sinuses involvement. The ethmoid (86.6%) and maxillary sinuses

(66.6%) were most commonly involved, followed by sphenoid sinus (23.3%). All patients were investigated by CT-scan and 11(36.7%) had central nervous system involvement, however, none underwent neurosurgical intervention. Seven patients (23.3%) had only sino-nasal and 23 (76.7%) had sino-orbital disease.

All patients received medical treatment while 28 (93.3%) underwent surgical intervention as well. The medical management consisted of amphotericin B deoxycholate. The lag time between onset of symptoms referable to zygomycosis and amphotericin B commencement ranged between 1 to 90 days with a median of 10 days. The median antifungal dose was 1000 mg (a range, 0-3300 mg) and median duration was 29 days (a range, 1-92 days). The median lag time between onset of symptoms and surgical management was 14 days (a range, 3-54 days). Surgical management ranged from debridement (12 cases), Caldwell-Luc operation (fenestration of the anterior wall of the maxillary sinus and the surgical drainage of this sinus into the nose via an antrostomy) (8 cases), frontoethmoidectomy (13 cases), middle meatal antrostomy (1 case), sphenoidectomy (4 cases), medial maxillectomy (10 cases), to orbital exenteration (13 cases). Number of surgical attempts was as follow: 13 patients (43.3%) once, 9 (30%) twice, 3 (10%) thrice, 2 (6.7%) five times and one patient seven times.

The predictors of survival included lag time between the first symptoms referable to zygomycosis and treatment with amphotericin B (p=0.01), dose of amphotericin B (p=0.00) and multiple surgical interventions (p=0.01).

Totally, 23 patients (76.7%) had orbital involvement. Visual changes and/or impairment of extraocular muscle function, as well as proptosis, ptosis, or periorbital cellulitis were not included in this category. Of 23 patients with orbital involvement, 10 died giving a mortality rate of 43.5%. In contrary, two patients without orbital involvement died giving a mortality rate of 28.6% (p=0.66). Orbital exenteration was performed in 13 patients (43.3%) with a mortality rate of 38.5%. The overall mortality rate was 40% (12 cases). Patients were followed for a median of 6 months (a range, 1-72 months). Associated predisposing factors of mortality are shown in table 2.

Table 2. Associated predisposing factors of mortality among patients with rhinocerebral zygomycosis

Condition	Death(%)	P-value
Male/female	35.3/46.2	0.71
Diabetes mellitus/Others	27.8/58.3	0.13
Orbital involvement/without orbital involvement	43.5/28.6	0.66
Multi-sinus involvement/one sinus involvement	33.3/35.7	0.23
WBC>10000/mm^3/ <10000/mm^3	52.9/23.1	0.14
One surgical attempt/ more than one surgical attempt	61.5/13.3	0.01

DISCUSSION

Rhinocerebral zygomycosis is the most common clinical syndrome of the diseases caused by fungi of the family mucoraceae (6). Zygomycosis typically originates in the nasal or oral mucosa, spreads to paranasal sinuses and enters to orbit via ethmoid and maxillary sinuses or via nasolacrimal ducts (2-5). Predisposing factors include hyperglycemia (due to uncontrolled diabetes or ketoacidosis), neutropenia associated with leukemia, lymphoma, corticosteroid therapy or other forms of immunesuppression, defroxamine therapy for iron overload, chronic sinusitis and intravenous drug abuse (2,4,5); but invasive zygomycosis forms may also, rarely, be seen in apparently healthy individuals.

Prior investigators demonstrated high percentage of diabetes as predisposing factor (75-95%) (1,7), however, some other published review articles with large sample size demonstrated lower frequency of DM (33-60%) (8,9), similar to ours (60%).

Red eye was the most common symptom followed by visual disturbance. Hence, these

symptoms should provoke diagnosis of zygomycosis especially in patients with diabetes or other predisposing factors. However, duration of diabetes and blood glucose level did not have any effect on prognosis in this study. Visual loss was reported in 53.3%, orbital involvement in 76.7% and surgical intervention in 93.3% of patients. These figures show the severity of disease in our patients.

Paranasal sinuses were involved in almost all patients and ethmoid (86.6%) and maxillary sinuses (66.6%) were the most commonly involved sinuses as indicated in other report (10).

All patients were treated with amphotericin B deoxycholate. Lipid soluble form of amphotericin B was not used because of its higher cost and lack of availability. Only two patients did not undergo surgical treatment and patients with more surgical interventions had better outcome.

Our documented mortality rate was 40%, a figure that is in agreement with others (1,11). Similar to Chamilos et al, we have found an association between delayed antifungal treatment and mortality (10,12). In our setting, mortality rate of diabetic patients (27.8%) was lower than others (58.3%), however, the difference was not statistically significant. This is in agreement with some other reports (6,8,9).

Institution of aggressive surgical debridement of devitalized tissue and systemic medical therapy is critical for good outcome (13,14). Patients who received more times of surgical treatment in addition to amphotericin B had a better outcome. These results highlight the importance of the timely initiation of a combination of aggressive surgical debridement and treatment with amphotericin B in patients with rhinocerebral zygomycosis

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