CRANIOCEREBRAL ASPERGILLOSIS OF SINONASAL ORIGIN IN IMMUNOCOMPETENT PATIENTS: CLINICAL SPECTRUM AND OUTCOME IN 25 CASES

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OBJECTIVE: Craniocerebral aspergillosis of sinonasal origin has been reported mainly in immunocompromised patients with high mortality, and it has been described very infrequently in immunocompetent hosts. This retrospective study focuses on clinical outcome in relation to anatomic locations of invasive aspergillosis of sinonasal origin in immunocompetent patients with emphasis on our preliminary experience with use of preoperative orally administered itraconazole.

METHODS: Medical records of patients treated in two tertiary care hospitals from 1991 to 2003 were reviewed retrospectively. All patients had radiological evidence of disease in the paranasal sinuses with or without intracranial extension. The study cohort was divided into three types on the basis of area of involvement revealed by computed tomographic or magnetic resonance imaging scans of brain. All patients underwent surgical intervention and treatment with antifungal therapy. Preoperative orally administered itraconazole therapy was used in four patients on the basis of neuroradiological features. Clinical outcome was assessed with the Glasgow Outcome Scale, and univariate analysis of prognostic factors was performed with 95% confidence interval ($P = 0.05$).

RESULTS: Mean patient age was 36.5 years (range, 14–74 yr) with a male preponderance (male-to-female ratio, 23:2). Nasal stuffiness (n = 13), headaches (n = 10), proptosis (n = 9), and nasal discharges (n = 7) were major presenting clinical features. Radiological data were obtained by computed tomographic (n = 25) and magnetic resonance imaging (n = 20) scans of the brain, and diagnoses were established by histopathological analysis (n = 20) or/and fungal cultures (n = 15). Preoperative orally administered itraconazole was given in four patients with intracerebral aspergillosis. Overall mortality was 28% and was highest in patients with Type 1 aspergillosis (66.7%). Type 3 aspergillosis and use of preoperative itraconazole remained statistically significant prognostic factors.

CONCLUSION: Craniocerebral aspergillosis in immunocompetent hosts has three patterns of presentation that seem to correlate with clinical outcomes. Intracerebral aspergillosis (Type 1) is associated with the worst clinical outcome. Patients with orbital and cranial base aspergillosis (Type 3) had good recovery. Intracranial extradural aspergillosis (Type 2) remained intermediate on the Glasgow Outcome Scale. Preoperative orally administered itraconazole therapy may improve clinical outcome in patients with intracerebral aspergillosis. Prospective clinical studies are required to make firm clinical therapeutic recommendations.

KEY WORDS: Aspergillosis, Clinical outcome, Immunocompetent hosts, Neuroradiological features, Orally administered itraconazole, Preoperative itraconazole

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Craniocerebral invasive aspergillosis of sinonasal origin is a challenging and increasingly encountered clinical entity in neurosurgical practice. The mortality rate is high despite advancement in surgical techniques and availability of more potent antifungal therapeutic agents (5, 9, 28, 38, 63). Most of the published clinical experience regarding management of invasive aspergillosis is derived from patients with significant immunodeficiency; data are scarce regarding

this relatively uncommon condition in immunocompetent hosts (2, 3, 16, 20, 28, 33).

The current standard therapeutic regimen for treatment of aspergillosis of sinocraniocerebral regions is radical surgery, then aggressive antifungal therapy with intravenously administered amphotericin B deoxycholate combined with or followed by flucytosine or itraconazole (14, 15, 33, 35, 36, 42, 43, 51, 54, 65). Since the introduction of itraconazole, the first azole with significant activity against *Aspergillus*, many multicenter clinical trials have proved its efficacy in combination or in sequential regimens (12, 14–16, 22, 24, 39, 47, 48, 54, 55). In addition to efficacy, the main advantage of itraconazole therapy compared with amphotericin B is that it is less toxic and better tolerated (12, 55, 62). Itraconazole has been reported to be effective in both prophylactic and treatment regimens in immunocompromised hosts with invasive aspergillosis (24, 48).

Newer triazoles, such as voriconazole, have been used as primary antifungal agents in invasive aspergillosis in immunocompromised patients. Voriconazole has proved to be more effective and less toxic than amphotericin B (25, 41). A few anecdotal reports have been published that describe treatment of intracranial *Aspergillus* abscesses in immunocompromised patients with liposomal amphotericin B combined with cytokine therapy and even with intracavitary amphotericin B (4, 10, 18).

This retrospective review describes our clinical experience with 25 cases of craniocerebral invasive aspergillosis in apparently nonimmunocompromised hosts. Patients were treated with subtotal excision and orally administered itraconazole therapy with or without preceding primary therapy with intravenously administered amphotericin B. The aims of this retrospective review are: 1) to present our clinical experience of invasive craniocerebral aspergillosis of sinonasal origin in immunocompetent patients; 2) to correlate the extent of disease and anatomic location of aspergillosis with clinical outcome; and 3) to assess our preliminary experience with preoperative orally administered itraconazole in such patients.

PATIENTS AND METHODS

Medical records of 25 patients with craniocerebral aspergillosis of sinonasal origin were reviewed retrospectively. Patients were treated in two major tertiary care teaching hospitals in Karachi, Pakistan, during the period from January 1991 to June 2003 (12.5 yr). These hospitals serve a large, mainly urban population of approximately 10 million people. This population is mixed, and almost all population subgroups of Pakistan are represented herein.

Inclusion/Exclusion Criteria

Clinical, radiological, and pathological records were reviewed for 134 patients who had been diagnosed as having invasive aspergillosis. The study included all patients of both sexes who: 1) were at least 14 years of age; 2) had radiological evidence of disease essentially in the nose and/or paranasal sinuses invading the orbit or the cranial base with or without extension into the cranial cavity (extradural location) and/or into the brain parenchyma (intradural location); 3) were immunocompetent as indicated by absence of any concomitant or previous chronic disease such as diabetes mellitus, renal failure, cirrhosis, malignancy or had a history of intravenous drug abuse, use of immunosuppressive or corticosteroid therapy, organ transplantation, or human immunodeficiency virus infection; 4) had no clinical and radiological evidence of systemic fungal infection such as pulmonary aspergillosis revealed by a routine chest x-ray; other screening tests, such as computed tomographic (CT) scans of the chest, were performed only if there was clinical suspicion of systemic/disseminated aspergillosis; and 5) had been proved to have invasive aspergillosis either by histopathological analysis or by culture, as opposed to having "allergic" sinus aspergillosis; patients with the latter condition were excluded. A total of 25 patients fulfilled these criteria.

Radiological Imaging and Anatomic Categorization

Axial and coronal CT scans of the brain and paranasal sinuses with or without contrast were performed in all patients. Coronal CT scans were obtained in 12 patients. Magnetic resonance imaging (MRI) of the brain was performed only in patients who presented with neurological symptoms. If an initial CT scan revealed orbital involvement, CT or MRI scans of the orbit also were obtained.

All patients had radiological evidence of disease in the nose and/or paranasal sinuses. On the basis of CT and MRI findings, we divided these patients into three types: 1) *Type 1 aspergillosis:* sinonasal disease with intracerebral aspergillosis without being contiguous; 2) *Type 2 aspergillosis:* sinonasal disease contiguous with intracranial extradural extension; and 3) *Type 3 aspergillosis:* sinonasal disease with only orbital and/or cranial base bony invasion/destruction.

Routine postoperative CT/MRI scans were performed after 3 months and then every 6 months. Early postoperative imaging scans were performed only in patients who had either persistent symptoms or recurrence of symptoms after appropriate management.

Surgical Intervention

In both the centers, patients were evaluated, diagnosed, and managed by a multidisciplinary "fungal team," which included consultants from neurosurgery; ear, nose, and throat; and infectious disease services. All our patients underwent surgical treatment either by ear, nose, and throat surgeons or by neurosurgeons, depending on the extent of disease. Transnasal debridement via fiberoptic endoscopic sinus surgery (n = 12) or transsphenoidal surgery (n = 2) was performed in patients who had the major bulk of fungal mass lying in nose and/or paranasal sinuses. Transcranial procedures (n = 9) were performed in all patients in whom the fungal mass was located in the brain parenchyma (Type 1 aspergillosis). In a

few patients, orbitotomies (n = 2) and ethmoidectomies (n = 3) were performed to achieve surgical resection of the *Aspergillus* mass.

Histomicrobiological Diagnosis

Diagnosis of aspergillosis was established by histopathological analysis and immunostaining of biopsied tissues (with periodic acid-Schiff and Grocott-Gomori methenamine-silver nitrate stains). Septate fungal hyphae branching at right angles were considered consistent with the diagnosis of aspergillosis. Tissue cultures and cerebrospinal fluid cultures also were performed. Twenty patients had histopathological findings, and cultures from 15 patients revealed *Aspergillus* growth. Therefore, 10 patients had diagnosis both by histopathological analysis and growth on cultures.

Antifungal Therapy

Intravenously administered amphotericin B deoxycholate (Fungizone; Bristol-Myers Squibb, Princeton, NJ) in a cumulative dose of 3 g was administered in divided doses during a 3- to 6-week period. The daily dose administered in our patients ranged from 0.5 to 2.5 mg/kg/d (with an initial single test dose of 0.1 mg/kg) and was titrated according to clinical tolerance and renal function of patients. The primary therapy with amphotericin B was followed by orally administered itraconazole 400 mg/d (Sporanox capsules; Janssen Pharmaceutica, Beerse, Belgium) in divided doses for 8 to 12 months. This regimen was administered to all patients having a more invasive disease pattern, as in Type 1 and Type 2 aspergillosis. In this manner, 11 patients (7 patients with Type 1 aspergillosis and 4 patients with Type 2 aspergillosis) received intravenously administered amphotericin B followed by orally administered itraconazole. Of these 11 patients, 6 patients tolerated the prescribed dose, and in 5 patients, amphotericin B therapy had to be discontinued because of progressive increase in serum creatinine levels. These patients were then continued with a regimen consisting only of orally administered itraconazole. All patients with Type 3 aspergillosis (n = 12) were treated with orally administered itraconazole for prolonged periods (to a maximum of 18 mo).

Patients with Type 1 (intracerebral) aspergillosis were treated for 2 to 3 weeks only with orally administered itraconazole therapy before surgical intervention. In these patients, the diagnosis was based on the peculiar neuroradiological features and anatomic location of the fungal mass. Postoperatively, two of these four patients received intravenously administered amphotericin B, then orally administered itraconazole (up to 12 mo). In the other two patients, only itraconazole was continued.

Antifungal therapy was monitored with serum creatinine levels and blood urea nitrogen every third day during first postoperative month and then once weekly during the rest of the prolonged treatment course. Liver function tests were performed only if there were persistent symptoms of nausea, vomiting, dyspepsia, and rigors during the course of itraconazole therapy. Orally administered itraconazole therapy was well tolerated in all patients (n = 19), and no patient developed clinically significant hepatic or renal toxicity. Patients who developed drug-induced nausea, vomiting, dyspepsia, and rigors were treated symptomatically.

Clinical Follow-up and Outcome Assessment

Clinical outcome was assessed with the Glasgow Outcome Scale (GOS) (30). Patients were followed-up in clinics after discharge from the hospital. In seven patients, telephonic contacts were used to assess the last best GOS score. The mean length of follow up was 10.6 months (range, 3–41 mo). Variables were computed and analyzed by use of SPSS software (Version 10.0; SPSS, Inc., Chicago, IL). Univariate analysis was performed for different prognostic factors in relation to the final GOS score by applying within-group variance (one-way analysis of variance). A P value of 0.05 was considered significant.

RESULTS

Demographic Characteristics and Clinical Presentation

Mean patient age at the time of presentation was 36.5 years (range, 14–74 yr) with a predominance of male patients (male-to-female ratio, 23:2). Clinical manifestations are tabulated for 25 patients in *Table 1*.

Radiological Findings

Routine chest x-rays (posteroanterior view) were performed in all patients to exclude pulmonary lesions of aspergillosis. CT scans of the chest were performed in only eight patients owing to clinical suspicion of pulmonary aspergillosis or *Aspergillus* infiltrates on the screening chest x-ray. Results were negative in all patients.

CT scans of the brain and paranasal sinuses were performed in all the patients. Bony erosion of sinus walls and/or cranial base was observed in 17 patients, and calcifications within the fungal mass were present in 3 patients. Contrast enhancement was observed on CT scans in 18 patients.

MRI scans of the brain were performed in 20 patients. The fungal mass lesions were extremely hypointense on T2-weighted images obtained in 18 patients and hypo- to isointense in 2 patients. On T1-weighted images, the lesions were isointense in 16 patients and hypo- to hyperintense in 2 patients. On T1-weighted gadolinium-enhanced images, the lesions revealed homogeneous bright enhancement. The diagnosis of aspergillosis was made if the lesion was extremely hypointense on T2-weighted images and revealed very bright, homogeneous contrast enhancement on postgadolinium T1-weighted sequences, especially with associated paranasal involvement.

TABLE 1. Summary of clinical manifestations in 25 patients

Clinical presentation	No. of patients
Nasal stuffiness	13
Headaches	10
Proptosis	9
Nasal discharge	7
Impaired consciousness	6
Periorbital pain	6
Diplopia	6
Anosmia	6
Papilledema	6
Cranial nerve deficits	6
Loss of vision	5
Local neurological deficits	4
Ophthalmoplegia	4
Fever	4
Malar swelling	2
Convulsions	1

Histomicrobiological Findings

Histopathological studies and immunostaining of fungal material revealed fungal hyphae branching at acute (45-degree) angles. Other prominent features included the presence of noncaseating granulomatous inflammation along with epithelioid and multinucleate giant cells. These were observed in all the biopsy specimens of 20 patients. Cultures of biopsies revealed growth of *Aspergillus flavus*. Cerebrospinal fluid cytological analysis was performed in two patients who underwent placement of ventriculoperitoneal shunts; results were normal and cultures revealed no fungal growth.

Management

Surgical intervention was performed in all 25 patients. The type and extent of surgery was determined according to anatomic location of the *Aspergillus* mass. *Tables 2* to *4* summarize the results of treatment for patients with each type of aspergillosis.

Six patients died during the course of amphotericin B treatment (mean duration, 2 wk; range, 1–3 wk). Mean duration of itraconazole therapy (whether alone or in combination) was 7.1 months (range, 3–18 mo) for all patients in the study (n = 25). Mean duration of itraconazole therapy was 7.7 months (range, 6–12 mo) for patients with Type 1 aspergillosis, 4.6 months (range, 3–6 mo) for patients with Type 2 aspergillosis, and 9.2 months (range, 3–18 mo) for patients with Type 3 aspergillosis. Similarly, in patients who survived during the study period (n = 18), mean duration of itraconazole was 8 months (range, 3–18 mo), and only one patient who received itraconazole therapy for 12 months died (Patient 6; *Table 2*).

TABLE 2. Clinical profile of patients with Type 1 aspergillosis[a]

Patient no.	Sex/age (yr)	Prediagnosis duration of symptoms (mo)[b]	Anatomic location	Antifungal therapy	GOS score	Follow-up
1	M/38	4	R medial temporal lobe	Amphotericin B	1	3 wk
2	M/39	4	R medial temporal lobe	Amphotericin B	1	1 wk
3	M/24	6	R parietal lobe	Amphotericin B	1	1 wk
4	M/16	2	L temporal lobe	Amphotericin B	1	3 wk
5	M/45	4	R subfrontal lobe	Amphotericin B	1	1 wk
6	M/42	1	L cavernous sinus, medial temporal lobe	Amphotericin B plus itraconazole[c]	1	16 mo
7	F/35	6	R temporal lobe	Amphotericin B plus itraconazole[c]	4	6 mo
8	M/38	6	R temporal lobe	Itraconazole[c]	4	6 mo
9	M/42	3	R frontotemporal lobe	Itraconazole[c]	4	8 mo

[a] GOS, Glasgow Outcome Scale; R, right; L, left.
[b] Mean duration of prediagnosis symptoms was 3.5 months (range, 1–6 mo; median, 4 mo). All patients underwent transcranial procedures.
[c] Orally administered itraconazole therapy started before surgical intervention.

TABLE 3. Clinical profile of patients with Type 2 aspergillosis[a]

Patient no.	Sex/age (yr)	Prediagnosis duration of symptoms (mo)[b]	Surgical procedure	Antifungal therapy	GOS score	Follow-up
1	M/40	8	Transsphenoidal resection	Amphotericin B + itraconazole[c]	5	6 mo
2	M/32	12	Bilateral FESS	Amphotericin B	1	3 wk
3	M/57	18	Bilateral FESS	Amphotericin B + itraconazole[c]	4	5 mo
4	M/74	20	Transsphenoidal resection	Amphotericin B + itraconazole[c]	4	3 mo

[a] GOS, Glasgow Outcome Scale; FESS, functional endoscopic sinus surgery.
[b] Mean duration of prediagnosis symptoms is 14.5 months (range, 8–20 mo; median, 15 mo).
[c] Orally administered itraconazole therapy.

TABLE 4. Clinical profile of patients with Type 3 aspergillosis[a]

Patient no.	Sex/age (yr)	Prediagnosis duration of symptoms (mo)[b]	Surgical procedure	Antifungal therapy	GOS score	Follow-up (mo)
1	M/16	8	FESS	Amphotericin B + itraconazole[c]	5	26
2	M/16	18	FESS + external ethmoidectomy (L)	Amphotericin B + itraconazole[c]	5	6
3	M/14	72	FESS	Amphotericin B + itraconazole[c]	5	10
4	M/53	12	External ethmoidectomy (R)	Amphotericin B + itraconazole[c]	4	5
5	M/30	18	FESS + lateral orbitotomy	Itraconazole[c]	5	16
6	M/14	12	FESS	Itraconazole[c]	5	12
7	M/30	14	FESS	Itraconazole[c]	5	17
8	M/38	12	External ethmoidectomy	Itraconazole[c]	5	41
9	M/28	18	Bilateral FESS	Itraconazole[c]	5	6
10	M/40	8	Bilateral FESS	Itraconazole[c]	5	12
11	M/45	12	Bilateral FESS	Itraconazole[c]	5	3
12	F/26	24	Bilateral FESS	Itraconazole[c]	5	4

[a] GOS, Glasgow Outcome Scale; FESS, functional endoscopic sinus surgery; L, left; R, right.
[b] Mean duration of prediagnosis symptoms is 19 months (range, 8–72 mo; median, 13 mo).
[c] Orally administered itraconazole therapy.

Complications

Two patients developed communicating hydrocephalus without clinical manifestations of meningitis. Cerebrospinal fluid cultures revealed no growth of *Aspergillus*, and the condition of both patients improved after placement of ventriculoperitoneal shunts. One patient developed multiple cerebral infarctions, one patient had intracerebral hemorrhage, and one patient developed widespread multifocal dissemination in the brain parenchyma and ventricles. All of these complications were observed in patients with Type 1 (intracerebral) aspergillosis within the first postoperative month.

Follow-up and Clinical Outcome

Mean duration of follow up for the cohort was 10.6 months (range, 3–41 mo). Seven patients died (28% mortality rate). Six of these patients died within the first 3 weeks after surgery; five of them had Type 1 aspergillosis and one had Type 2 aspergillosis. One patient survived for 16 months (Patient 6).

Three patients with Type 1 aspergillosis had moderate disability. In Type 2 aspergillosis, good recovery (GOS score, 5) was observed in one patient, and moderate disability (GOS score, 4) was documented in two patients. In patients with Type 3 aspergillosis, good recovery was documented in 11

patients, and moderate disability was observed in one patient. In the cohort of 25 patients, good recovery was documented in 48% (n = 12), and moderate disability was present in 24% (n = 6). Mortality in the group of patients with Type 1 (intracerebral) aspergillosis was 66.7% (n = 6), and mortality was 25% (n = 1) in patients with Type 2 aspergillosis. *Tables 2* to *4* summarize the clinical outcome according to GOS in patients with each type of aspergillosis.

For treatment of Type 1 aspergillosis, four patients (Patients 6–9) received preoperative itraconazole therapy. Three of these patients had moderate disability (GOS score, 4), and one patient died (GOS score, 1) after surviving for 16 months. It is notable that other five patients with Type 1 aspergillosis died within 3 weeks postoperatively.

No patient with Type 3 aspergillosis died. A summary of univariate analysis of different factors in relation to clinical outcome is shown in *Table 5*. Type 1 aspergillosis ($P = 0.000$) and use of preoperative itraconazole therapy ($P = 0.05$) were statistically significant prognostic factors affecting clinical outcome.

DISCUSSION

Craniocerebral invasive aspergillosis accounts for 5% of all intracranial fungal infections, and it has been reported more frequently in recent literature (2, 28, 51, 65). Clinical outcomes of craniocerebral aspergillosis in immunosuppressed and apparently immunocompetent hosts are different owing to the severity of the infective process and variable immune response (14, 17, 27–29, 33, 43, 44, 58). Case series of craniocerebral aspergillosis in immunocompetent hosts have been reported mainly from Pakistan, India, Saudi Arabia, Sudan, and other African countries (1, 9, 23, 27, 28, 42, 43, 57, 61). This apparent prevalence in immunocompetent hosts is thought to be attributable to tropical environmental conditions (hot and dry), bad hygiene, and poor socioeconomic status (1, 9, 31, 57). In our series, craniocerebral aspergillosis predominantly affected middle-aged men, which is different from populations affected with the disease in other reported series (27, 34, 42, 43). The male preponderance possibly is caused by local socioeconomic conditions in Pakistan, where males are more exposed to external environmental pollutants.

Pathophysiology

Hora and Houston (26) first recognized primary aspergillosis of paranasal sinuses, which can be noninvasive or invasive. Current studies distinctly divide aspergillosis of sinonasal origin into noninvasive (also called allergic *Aspergillus* sinusitis) and invasive forms, with separate treatment modalities (35, 37, 38, 46, 59). The invasive type may present with extension into the orbit or cranial cavity, and it manifests radiologically as a paranasal mass contiguous with extension into the orbital or cranial cavity (6, 27, 36, 38, 43, 50, 57, 63).

The impetus for a saprophytic colony of paranasal sinus aspergillosis to become pathogenic is the mechanical obstruction of the nose and paranasal sinuses (50). This can occur secondary to septal deviation, nasal polyps, infections, and allergic rhinosinusitis (38). Location has been cited as the cause of the more aggressive nature of sphenoid aspergillosis, i.e., its close relationship to cranial base (6, 38, 50). However, erosion of bone is not always necessary for the development of intracranial extension, as the aspergillosis has the propensity to spread along vessels that serve as direct channels for the seeding of aspergilli (13, 38, 50). This seems to be mode of spread for aspergillosis in our patients with intracerebral aspergillosis. Regarding a mechanism of damage at the cellular level in cerebral *Aspergillus* lesions, recent in vitro results implicated secretion of various necrotizing factors with toxic and lytic activity toward neurons and glial cells (40, 53).

Chiller et al. (7, 8) recently developed an animal (murine) model of cerebral aspergillosis, which may be helpful in studying the relevant immune mechanisms and may provide a guide to evaluate the efficacy of different treatment modalities. The mechanism causing invasiveness of aspergillosis in immunologically competent hosts remains unclear. It is possibly caused by qualitative cellular or subcellular immunodeficiency that is either unrecognized or poorly characterized (17, 45). The patients in our study were immunologically

TABLE 5. Statistical distribution of prognostic factors by responding versus nonresponding groups

Responders		Nonresponders	
Prognostic factors	***P* value[a]**	**Prognostic factors**	***P* value[a]**
Prediagnosis duration of symptoms (6 mo)	0.398	Type 3 aspergillosis (n = 12)[b]	0.000
Type 2 aspergillosis (n = 4)[b]	0.574	Use of preoperative itraconazole therapy (average, 1 mg/kg protein in 4 patients)	0.05
Type 1 aspergillosis (n = 9)[b]	0.638		
Duration of itraconazole therapy (average, 4 wk)	0.246		

[a] *P* value of 0.05 with 95% confidence interval is considered significant.
[b] Clinical outcome assessed at 3 months after the diagnosis.

competent on the basis of clinical and radiological evidence, yet they had developed advanced, locally invasive aspergillosis. Another notable pathological finding is formation of granulomas and the presence of epithelioid and multinucleate giant cells in these patients (18, 33). This indicates at least some integrity of immune response, which supports the clinical diagnosis of immunocompetence.

Aspergillus flavus is the only causative agent noted in all culture-proven cases in our series; in contrast, *Aspergillus fumigatus* is more frequently observed in immunocompromised patients with invasive aspergillosis. We think there may be two reasons for this. First, *A. flavus* species is the most common cause of fungal sinusitis (26, 31, 37, 38, 46, 59). Second, it is also the most frequent species isolated in cultures of invasive aspergillosis of nasal and paranasal origin in patients from hot and dry environment such as Africa, Saudi Arabia, and the Indian subcontinent (1, 31, 42, 43, 49, 57). *A. flavus*, which has saprophytic characteristics, has a particular propensity to grow and flourish in the microaerophilic environment of the nasal and paranasal sinuses in hot and dry climatic conditions (1, 26, 37, 38, 43).

Radiological Imaging

CT findings of a hyperdense mass lesion in the paranasal sinuses with bony expansion/destruction and extending into the orbitocranial compartments *(Figs. 1–3)* are features suggestive of invasive aspergillosis (6, 27, 43, 52). On MRI scans, an *Aspergillus* mass was extremely hypointense on T2-weighted sequences and hypointense to isointense on T1-weighted images; it revealed bright homogeneous enhancement with contrast administration (11, 13, 52, 64). We determined that these neuroradiological features and anatomic location provide sufficient empirical reason to start antifungal therapy before surgery without pathological diagnosis. This is analogous to clinical practice in our location for treatment of neurotuberculosis; characteristic radiological appearance of lesion with clinical features in an endemic area is usually sufficient for antituberculous treatment to be started. Histopathological and/or microbiological confirmation is not required, as clinical response justifies this approach in most cases.

Surgical Intervention

Radical surgical excision followed by aggressive antifungal chemotherapy is the mainstay of treatment in invasive aspergillosis (1, 14, 15, 35, 42, 43, 54, 65). Naim-Ur-Rahman et al. (43) observed that radical surgery during an earlier stage and as a first procedure is better than repeated attempts at subradical resection. In our experience, however, radical excision of fungal mass does not seem to be necessary. Radical surgery involving risks of morbidity seems excessive for an infective process. Subradical excision aimed at reducing surgical morbidity in combination with systemic/orally administered antifungal therapy seems to be a better course of action.

We think that clearing the nasal passages is necessary to deprive the fungus of a microaerophilic environment. This

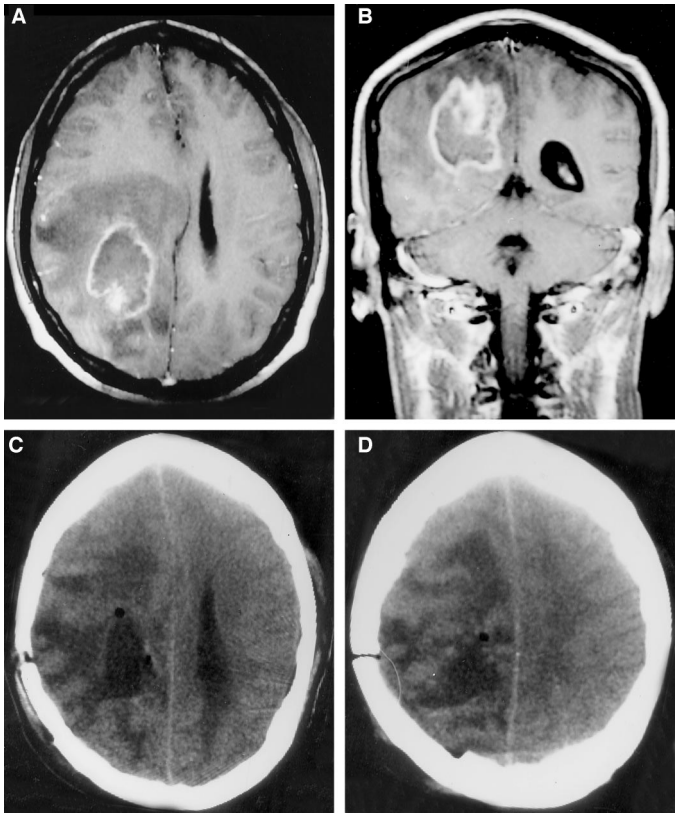

FIGURE 1. A, *post-gadolinium T1-weighted axial MRI scan showing a mass lesion located in the right parieto-occipital region with peripheral ring enhancement and central nonenhancing area. The mass with perifocal edema is producing significant mass effect and midline shift.* B, *gadolinium-enhanced T1-weighted MRI scan of the same patient, showing the same lesion in coronal view. The lesion has irregular margins and it obliterates the ipsilateral lateral ventricle.* C *and* D, *postcraniotomy nonenhancing axial CT scans of the same patient, showing significant edema and mass effect. This patient's condition deteriorated rapidly after surgery. The patient died within 1 week of surgical intervention.*

usually will lead to gradual necrosis of the fungus in the paranasal sinuses. Therefore, this procedure probably needs to be performed in every case of sinonasal aspergillosis. It may be required repeatedly as necessary.

Surgical techniques tailored according to anatomic location and extent of disease should be used. We also think that stereotactic aspiration or biopsy (21, 32) of the mass is not sufficient, as the *Aspergillus* hyphae are only present in the rim of tissue around the lesion.

Antifungal Therapy

For invasive aspergillosis, response to antifungal triazoles such as itraconazole and voriconazole is sometimes superior to that achieved with conventional intravenously administered amphotericin B, even as a primary antifungal therapy (16, 24, 25, 47). It has been demonstrated that treatment of cerebral aspergillosis with high-dose, orally administered itraconazole improves prog-

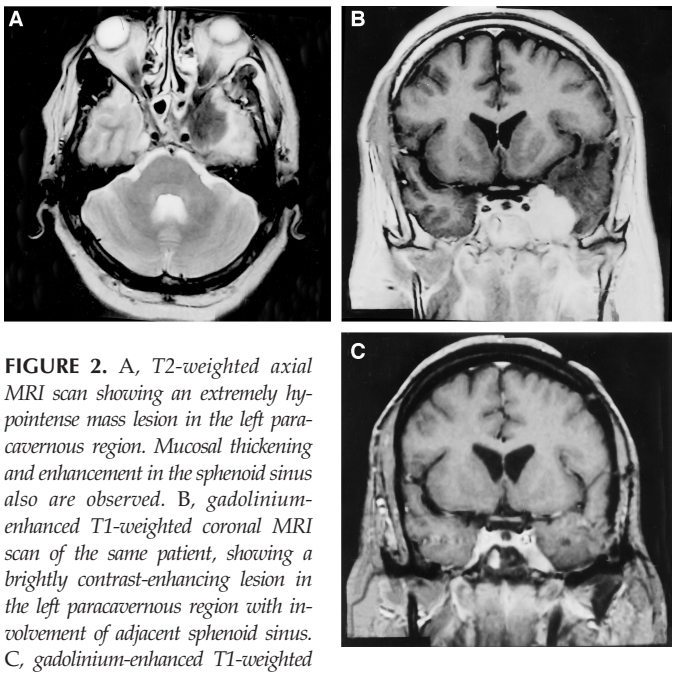

FIGURE 2. A, *T2-weighted axial MRI scan showing an extremely hypointense mass lesion in the left paracavernous region. Mucosal thickening and enhancement in the sphenoid sinus also are observed.* B, *gadolinium-enhanced T1-weighted coronal MRI scan of the same patient, showing a brightly contrast-enhancing lesion in the left paracavernous region with involvement of adjacent sphenoid sinus.* C, *gadolinium-enhanced T1-weighted coronal MRI scan of the same patient 6 months after craniotomy, showing significant reduction in the size of lesion. This patient received a 2-week regimen of itraconazole preoperatively, then combined amphotericin B (cumulative dose of 3 g in 4 wk) and itraconazole. Itraconazole was continued for 12 months, and the patient has survived with moderate disability (GOS score, 4).*

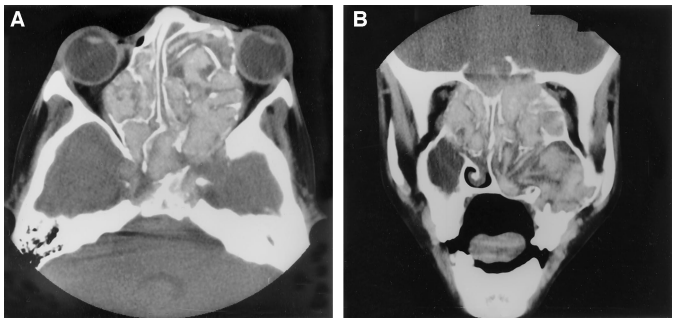

FIGURE 3. A, *postcontrast axial CT scan showing a contrast-enhancing mass, which is producing bone destruction and extending the orbital cavities more on the left side.* B, *postcontrast coronal CT scan of the same patient, showing bony destruction of the cranial base. This patient underwent fiberoptic endoscopic sinus surgery, was treated with orally administered itraconazole therapy for 12 months, and had a good recovery (GOS score, 5).*

nosis, especially if conventional therapy has failed (47, 48). During the course of this study, preoperative orally administered itraconazole was started empirically on the basis of diagnostic neuroradiological features of aspergillosis. This therapeutic regimen was used in four patients with Type 1 (intracerebral) aspergillosis (Patients 6–9). We demonstrated that it improved GOS scores (moderate disability in three patients), reduced mortality (one of four patients died), and prolonged survival (Patient 6 survived for 16 mo).

Orally administered itraconazole in capsule formulation has been used successfully for many years. Recently, it was demonstrated to be an effective preparation in neutropenic patients, but it has variable and inconsistent absorption in some patients (12, 44). This has led to the production of newer formulations (by adding cyclodextrin) in the form of orally administered solution and intravenous preparations (12, 62). Neither orally administered solution nor intravenously administered itraconazole are available in Pakistan, so we used itraconazole in capsule form. It has been well tolerated in all our patients and has demonstrated good clinical response.

Clinical Outcome and Mortality

The overall mortality in our series was 28%, which is lower than that described in other series of aspergillosis in immunocompetent patients (28, 42, 43). Mortality in intracerebral aspergillosis (in immunocompromised hosts) is reported to reach 100% (14, 15). In our experience, mortality was 66.7% in Type 1 (intracerebral) aspergillosis, and it was 25% in Type 2 aspergillosis. No patient died who had Type 3 aspergillosis. Similarly, good recovery and moderate disability scores were better in patients with Type 2 and Type 3 aspergillosis. Clinical outcome in extradural aspergillosis (Type 3) is better than in patients with intracerebral (intradural) involvement (Type 1), but clinical outcome is intermediate in intracranial extradural aspergillosis (Type 2).

The cerebrovascular complications caused by angioinvasive predilection of aspergillosis have been well described (19, 56, 60). Poor outcome in intradural aspergillosis (Type 1) may be attributable to subclinical or occult angioinvasion, which results in fatal catastrophic cerebrovascular manifestations. Most of our patients died of angioinvasive complications that include intracerebral hemorrhage, infarction, and intracerebral dissemination.

Limitations of Study

Although reasonably strict criteria for establishing immunocompetence were used, laboratory evidence of immunocompetence was not available. Follow-up was not sufficient in all patients. As a retrospective study, this case series can provide only limited evidence for therapeutic recommendations.

CONCLUSION

Craniocerebral aspergillosis of sinonasal origin in immunocompetent hosts has three patterns of presentation, depending on the anatomic distribution of disease, which seem to correlate with final clinical outcome. Intracerebral aspergillosis (Type 1) is associated with the worst clinical outcome, and patients with orbital and cranial aspergillosis (Type 3) have experienced good recovery. Intracranial extradural aspergillosis (Type 2) is intermediate on the clinical outcome scale. Adequate surgical excision combined with aggressive antifungal therapy remains the cornerstone of management. Our experience indicates that preoperative optimization with

orally administered itraconazole therapy may improve clinical outcome of the more invasive and intradural type of aspergillosis (intracerebral aspergillosis). Prospective clinical studies are required to make firm clinical therapy recommendations.

REFERENCES

1. Alrajhi AA, Enani M, Mahasin Z, Al-Omran K: Chronic invasive aspergillosis of the paranasal sinuses in immunocompetent hosts from Saudi Arabia. **Am J Trop Med Hyg** 65:83–86, 2001.
2. Artico M, Pastore FS, Polosa M, Sherkat S, Neroni M: Intracerebral aspergillus abscess: Case report and review of the literature. **Neurosurg Rev** 20:135–138, 1997.
3. Brid NS, Kulkarni AG, Kale MM, Shah PJ, Yaav SR: Ring-enhancing lesions on computed tomography. **Postgrad Med J** 73:355–356, 1997.
4. Camarata PJ, Dunn DL, Farney AC, Parker RG, Seljeskog EL: Continual intracavitary administration of amphotericin B as an adjuvant in the treatment of aspergillus brain abscess: Case report an review of literature. **Neurosurgery** 31:575–579, 1992.
5. Casey AT, Wilkins P, Uttley D: Aspergillosis infections in neurosurgical practice. **Br J Neurosurg** 8:31–39, 1994.
6. Centeno RS, Bentson JR, Mancuso AA: CT scanning in rhinocerebral mucormycosis and aspergillosis. **Radiology** 140:383–389, 1981.
7. Chiller TM, Luque JC, Sobel RA, Farrokhshad K, Clemons KV, Stevens DA: Development of a murine model of cerebral aspergillosis. **J Infect Dis** 186:574–577, 2002.
8. Chiller TM, Luque JC, Sobel RA, Farrokhshad K, Clemons KV, Stevens DA: Efficacy of amphotericin B or itraconazole in a murine model of central nervous system *Aspergillus* infection. **Antimicrob Agents Chemother** 47: 813–815, 2003.
9. Chugh KS, Sakhuja V, Jain S, Talwar P, Minz M, Joshi K, Indudhara R: High mortality in systemic fungal infections following renal transplantation in third-world countries. **Nephrol Dial Transplant** 8:168–172, 1993.
10. Coleman JM, Hogg GG, Rosenfeld JV, Waters KD: Invasive central nervous system aspergillosis: Cure with liposomal amphotericin B, itraconazole, and radical surgery—A case report and review of the literature. **Neurosurgery** 36:858–863, 1995.
11. Cox J, Murtagh FR, Wilfong A, Brenner J: Cerebral aspergillosis: MR imaging and histopathological correlation. **AJNR Am J Neuroradiol** 13:1489–1492, 1992.
12. De Beule K, Gestel JV: Pharmacology of itraconazole. **Drugs** 61[Suppl 1]:27–37, 2001.
13. Delone DR, Goldstein RA, Petermann G, Salamat S, Miles JM, Knechtle SJ, Brown WD: Disseminated aspergillosis involving the brain: Distribution and imaging characteristics. **AJNR Am J Neuroradiol** 20:1597–1604, 1999.
14. Denning DW: Therapeutic outcome in invasive aspergillosis. **Clin Infect Dis** 23:608–615, 1996.
15. Denning DW, Stevens DA: Antifungal and surgical treatment of invasive aspergillosis: Review of 2121 published cases. **Rev Infect Dis** 12:1147–1201, 1990.
16. Denning DW, Hostetler JS, Kauffman CA: NIAID Mycoses Study Group Multicenter Trail of Oral Itraconazole Therapy for Invasive Aspergillosis. **Am J Med** 97:135–144, 1994.
17. Diamond RD, Krzesicki R, Epstein B, Jao W: Damage to hyphal forms of fungi human leukocytes in vitro: A possible host defense mechanism in aspergillosis and mucormycosis. **Am J Pathol** 91:313–328, 1978.
18. Ellis M, Watson R, Mcnabb A, Lukic L, Nork M: Massive intracerebral aspergillosis responding to combination high dose liposomal amphotericin B and cytokine therapy without surgery. **J Med Microbiol** 51:70–75, 2002.
19. Endo T, Tominaga T, Konno H, Yoshimoto T: Fatal subarachnoid hemorrhage, with brainstem and cerebellar infarction, cause by aspergillus infection after cerebral aneurysm surgery: Case report. **Neurosurgery** 50:1147–1150, 2002.
20. Erdogan E, Beyzadeoglu M, Arpaci F, Celasun B: Cerebellar aspergillosis: Case report and literature review. **Neurosurgery** 50:874–876, 2002.
21. Goodmann ML, Coffey RJ: Stereotactic drainage of aspergillus brain abscess with long-term survival: Case report and review. **Neurosurgery** 24:96–98, 1989.
22. Hakim SM, Milne LJ, Fox C, Nawroz IM, Vaughan GT, Webb G: Management of invasive aspergillosis with itraconazole. **Br J Clin Pract** 47:312–314, 1993.
23. Haran RP, Chandy MJ: Intracranial aspergillus granuloma. **Br J Neurosurg** 7:383–388, 1993.
24. Harousseau JL, Dekker AW, Stamatoullas-Bastard A, Fassas A, Linkesch W, Gouveia J, De Bock R, Rovira M, Seifert WF, Joosen H, Peeters M, De Beule K: Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: A randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin B. **Antimicrob Agents Chemother** 44:1887–1893, 2000.
25. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, De Pauw B: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. **N Engl J Med** 347:408–415, 2002.
26. Hora JF, Houston FS: Primary aspergillosis of the paranasal sinuses and associated areas. **Laryngoscope** 74:768–773, 1965.
27. Hussain S, Salahuddin N, Ahmad I, Salahuddin I, Jooma R: Rhinocerebral invasive mycosis: Occurrence in immunocompetent individuals. **Eur J Radiol** 20:151–155, 1995.
28. Jamjoom AB, Al-Hedaithy SA, Jamjoom ZA, Al-Hedaithy M, El-Watidy SF, Naim-Ur-Rahman, Al-Moallem M: Intracranial mycotic infections in neurosurgical practice. **Acta Neurochir (Wien)** 137:78–84, 1995.
29. Jantunen E, Volin L, Salonen O, Piilonen A, Parkkali T, Anttila A, Paetau A, Ruutu T: Central nervous system aspergillosis in allogeneic stem cell transplant recipients. **Bone Marrow Transplant** 31:191–196, 2003.
30. Jennett B, Bond M: Assessment of outcome after severe brain damage: A practical scale. **Lancet** 1:480–484, 1975.
31. Kameswaran M, al-Wadei A, Khurana P, Okafor BC: Rhinocerebral aspergillosis. **J Laryngol Otol** 106:981–985, 1992.
32. Kerkmann ML, Blaschke-Hellmessen R, Mikulin HD: Successful treatment of cerebral aspergillosis by stereotactic operation and antifungal therapy. **Mycoses** 37:123–126, 1994.
33. Kim DG, Hong SC, Kim HJ, Chi JG, Han MH, Choi KS, Han H: Cerebral aspergillosis in immunologically competent patients. **Surg Neurol** 40:326–331, 1993.
34. Kleinschmidt-DeMasters BK: Central nervous system aspergillosis: A 20-year retrospective series. **Hum Pathol** 33:116–124, 2002.
35. Kontoyiannis DP, Bodey GP: Invasive aspergillosis in 2002: An update. **Eur J Clin Microbiol Infect Dis** 21:161–172, 2002.
36. Kurita H, Shiokawa Y, Furuya K, Segawa H, Sano K: Parasellar aspergillus granuloma extending from the sphenoid sinus: Report of two cases. **Surg Neurol** 44:489–494, 1995.
37. Marple BF: Allergic fungal rhinosinusitis: Current theories and management strategies. **Laryngoscope** 111:1006–1019, 2001.
38. McGill TJ, Simpson G, Healy GB: Fulminant aspergillosis of the nose and paranasal sinuses: A new clinical entity. **Laryngoscope** 90:748–754, 1980.
39. Mikolich DJ, Kinsella LJ, Skowron G, Friedman J, Sugar AM: Aspergillus meningitis in immunocompetent adults successfully treated with itraconazole. **Clin Infect Dis** 23:1318–1319, 1996.
40. Moris JH: The nervous system, in Cotran RS, Kumar V, Robbins SL (eds): *Robbins Pathological Basis of Disease*. Philadelphia, W.B. Saunders Co., 1989, ed 4, pp 1385–1449.
41. Muijsers RB, Goa KL, Scott LJ: Voriconazole in the treatment of invasive aspergillosis. **Drugs** 62:2655–2664, 2002.
42. Murthy JM, Sundaram C, Prasad VS, Purohit AK, Rammurti S, Laxmi V: Aspergillosis of central nervous system: A study of 21 patients seen in a university hospital in south India. **J Assoc Physicians India** 48:677–681, 2000.
43. Naim-Ur-Rahman, Jamjoom A, Al-Hedaithy SA, Jamjoom AB, Al-Sohaibani MO, Aziz SA: Cranial and intracranial aspergillosis of sino-nasal origin: Report of nine cases. **Acta Neurochir (Wien)** 138:944–950, 1996.
44. Nucci M, Biasoli I, Akiti T: A double blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients. **Clin Infect Dis** 30:300–305, 2000.
45. Pagani A, Spalla R, Ferrari FA, Duse M, Lenzi I, Bretz U, Baggiolini M, Siccardi AG: Defective aspergillosis killing by neutrophil leucocytes in a case of systemic aspergillosis. **Clin Exp Immunol** 43:201–207, 1981.

46. Romero Maura JM, Bori Aiguavella MA, Fontana M, Escolan Gelos A, Abascal: Aspergillosis of the paranasal sinuses [in Spanish]. **An Otorrinolaringol Ibero Am** 25:113–119, 1998.
47. Rowe-Jones JM, Freedman AR: Adjuvant itraconazole in the treatment of destructive sphenoid aspergillosis. **Rhinology** 32:203–207, 1994.
48. Sanchez C, Mauri E, Dalmau D, Quintana S, Apatricio A, Garau J: Treatment of cerebral aspergillosis with itraconazole: Do high doses improve the prognosis? **Clin Infect Dis** 21:1485–1487, 1995.
49. Sanghvi V, Bokil K, Kelkar R: Aspergillosis of the paranasal air sinuses: Case reports and review of literature. **Indian J Cancer** 29:7–13, 1992.
50. Sarti EJ, Blaugrund SM, Lin PT, Camins MB: Paranasal sinus disease with intracranial extension: Aspergillosis versus malignancy. **Laryngoscope** 90: 748–754, 1988.
51. Sobel JD: Practice guideline for the treatment of fungal infections. **Clin Infect Dis** 30:652–656, 2000.
52. Som PM, Dillion WP, Curtin HD, Fullerton GD, Lidov M: Hypointense paranasal sinus foci: Differential diagnosis with MR imaging and relation to CT finding. **Radiology** 176:777–781, 1990.
53. Speth C, Rambach G, Lass-Flörl C, Würzner R, Gasque P, Mohsenipour I, Dierich MP: Culture supernatants of patient-derived aspergillus isolates have toxic and lytic activity towards neurons and glial cells. **FEMS Immun Med Microbiol** 29:303–313, 2000.
54. Steinbach WJ, Stevens DA, Denning DA: Combination and sequential antifungal therapy for invasive aspergillosis: Review of published in vitro and in vivo interactions and 6281 clinical cases from 1966 to 2001. **Clin Infect Dis** 37[Suppl 3]:S188–S224, 2003.
55. Stevens DA, Lee JY: Analysis of compassionate use itraconazole therapy for invasive aspergillosis by the NIAID Mycoses Study Group criteria. **Arch Intern Med** 157:1857–1862, 1997.
56. Takeshita M, Izawa M, Kubo O, Tanikawa T, Onda H, Wanifuchi H, Tamura Y, Kagawa M: Aspergillotic aneurysm formation of cerebral artery following neurosurgical operation. **Surg Neurol** 38:146–151, 1992.
57. Tierney P, Thomas M, Samuel D, Patel KS, Stafford N: Recurrent aspergilloma of the frontoethmoid sinus in a non-immunocompromised patient. **J R Soc Med** 89:165–166, 1996.
58. Torre-Cisneros J, Lopez OL, Kusne S: CNS aspergillosis in organ transplantation: A clinicopathological study. **J Neurol Neurosurg Psychiatry** 56:188–193, 1993.
59. Tsimikas S, Hollingsworth HM, Nash G: Aspergillus brain abscess complicating allergic sinusitis. **J Allergy Clin Immunol** 94:264–267, 1994.
60. Viriyavejakul P, Phudhichareonrat S, Boonpasat Y, Viriyavejakul A, Rojanasunan P, Phophak N, Pattanasak N: Intracerebral hemorrhage due to nosocomial aspergillosis following neurosurgery. **Southeast Asian J Trop Med Public Health** 30:154–156, 1999.
61. Walsh TJ, Hier DB, Caplan LR: Aspergillosis of the central nervous system:Clinicopathological analysis of 17 patients. **Ann Neurol** 18:574–582, 1985.
62. Willems L, van der Geest R, de Beule K: Itraconazole oral solution and intravenous formulations: A review of pharmacokinetics and pharmacodynamics. **J Clin Pharm Ther** 26:159–169, 2001.
63. Wilson M, Denning DW: The commonest life-threatening mold infection: Invasive aspergillosis. **Hosp Update** 19:225–233, 1993.
64. Yamada K, Shrier DA, Rubio A, Shan Y, Zoarski GH, Yoshiura T, Iwanaga S, Nishimura T, Numaguchi Y: Imaging findings in intracranial aspergillosis. **Acad Radiol** 9:163–171, 2002.
65. Young RF, Gade G, Grinnel V: Surgical treatment for fungal infections in the central nervous system. **J Neurosurg** 63:371–381, 1985.

COMMENTS

The authors describe the clinical presentation and outcome of a series of 25 immunocompetent patients with neuroaspergillosis who were managed with antifungal therapy and surgery. As expected, the prognosis and mortality (76%) were worse for those patients with intracerebral fungal involvement. Those patients with infection confined to the nose and orbit who received itraconazole fared the best to a statistically significant degree. These results are not unexpected, because of the known inability of amphotericin B to cross the blood-brain barrier, which is not necessary for those with only cranial base and orbital involvement. The preoperative addition of orally administered itraconazole provides a new twist for the management of this difficult neurosurgical problem, which is often associated with a poor outcome in both immunocompromised and immunocompetent patients. In fact, some patients with intracerebral disease were pretreated with itraconazole for 2 to 3 weeks before surgical intervention. Although surgery is essential in the management of this disease, this report diminishes the urgency of surgery so long as antifungal therapy is being administered. Whether itraconazole will change the course of the disease for patients with intracerebral involvement needs to be seen but is certainly worth exploring on the basis of the promising results demonstrated in this preliminary report. Itraconazole is usually well tolerated and has few side effects, which are mostly gastrointestinal in origin, such as nausea, vomiting, and constipation. Less common side effects are headache, dizziness, pruritus, skin rash, and rarely, a Stevens-Johnson syndrome. In this series, the drug was well tolerated without renal or hepatic toxicity, and all other side effects were managed symptomatically.

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In this article, Siddiqui et al. have presented a large series of patients with cranial aspergillosis. What is unusual compared with most reports on this topic is that the patients were not immunocompromised. Patients with infection limited to the nasal/orbital regions and those with contiguous extradural spread fared well, with 15 (94%) of 16 patients having a Glasgow Outcome Scale score of 4 or 5. Conversely, six of nine patients with parenchymal disease died despite appropriate treatment. The authors have presented a thoughtful analysis.

Bruce E. Pollock
Rochester, Minnesota

The authors have performed a great service by compiling much of the journal-published English-language literature on surgical management of traumatic brain injury. They have highlighted the limited quality of that evidence and yet identified a great deal of information that has made it possible to gradually improve the care of these patients. They have wisely avoided identifying these as evidence-based guidelines, because of both the methodological limitations of the review and the primary data. However, as a repository of the best evidence that is available to guide the surgical treatment of patients with traumatic brain injury, this document is a major step forward. As a guide to the need for further, higher-quality, clinical research in traumatic brain injury, it is unsurpassed.

The lack of high-quality evidence to support the authors' recommendations has two important implications. First, it must not be forgotten that evidence of this quality leaves room for, indeed requires, flexibility in individual physician interpretation and

application to specific clinical situations. It would be as bad a mistake to interpret the recommendation to evacuate subdurals with midline shift greater than 5 mm as an absolute requirement as it would be to fail to remove an epidural hematoma in a patient with neurological deterioration simply because it was less than 30 cm^3 in volume. Second, this compilation provides an eloquent and urgent plea for more cooperation among neurosurgeons to perform the kind of high-quality clinical research that can answer questions as well as raise them.

Stephen J. Haines
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In this work, Siddiqui et al. report their retrospective 12-year experience with craniocerebral aspergillosis in immunocompetent patients in two tertiary care hospitals in Pakistan. There is a scarcity of data and no organized clinical experience about the management of this relatively uncommon entity. Because most of the experience is derived from patients with significant immunosuppression, there is a clear need for information about the management of this infection in the immunocompetent host. In that regard, this article provides useful information. However, some of the evidence presented is not always complete to arrive at a generalizable conclusion.

The article describes a selected group of patients: predominantly middle-aged men from a developing country. The mechanism of their progressive, invasive infection is unclear and could be a result of subtle dysfunction in key effector immune cells, such as macrophages or T-cell subsets. Patients with other well-described risk factors for craniocerebral aspergillosis in the "immunocompetent" host, such as head trauma, intravenous drug abuse, postoperative nosocomial infections complicating neurosurgical operations, endocarditis, and significant comorbidity such as diabetes, severe malnutrition, or cirrhosis (7) have been excluded from this cohort. Nevertheless, the underlying risk factors for craniocerebral aspergillosis in "immunocompetent" hosts contrast to the risk factors for that entity in immunosuppressed patients, typically patients with hematological malignancy or transplantation in which neutropenia and significant corticosteroid use predominate as risk factors.

Remarkably, no patient in the cohort had multiple brain lesions. Subarachnoid hemorrhage, concomitant endophthalmitis, stroke, or a combination of both alterations of mental status and neurological deficits at presentation: these presenting symptoms are more common in immunosuppressed patients and are prognostic factors for poor outcome. The authors could also comment on the effect of predisposing factors and the mechanism of spread of the infection on its chronic or acute course. For example, some of their patients had a recently described (3) distinct intracranial perineural extension of *Aspergillus* rhinosinusitis, but it is unclear whether that presentation carried a difference in prognosis in this series.

Some of the patients in this study were diagnosed by histopathology only (culture was negative) that showed acute-angle branching hyphae consistent with aspergillosis. The degree of immunosuppression (or lack thereof) affects the appearance of *Aspergillus*-induced lesions in the brain. The less immunosuppressed the patient is, the more granulomatous formation is appreciated, as shown in this study. However, other hyalohyphomycetes, such as *Fusarium* species or *Scedosporiumi* species, have indistinguishable appearance in tissues. This is clinically important, because itraconazole has no activity against these molds. Most of the culture-proven cases were caused by *Aspergillus flavus* and not *A. fumigatus*, the most common cause of invasive aspergillosis in general. This is not surprising, because *A. flavus* is the most common cause of *Aspergillus* sinusitis because it has bigger conidia than *A. fumigatus*.

Despite the positive results described here with itraconazole tablets, the usefulness of itraconazole for sinocranial aspergillosis is controversial; these are the two sites at which most failures have been described in the National Institute of Allergy and Infectious Diseases Mycosis Study Group compassionate trial (5). Most experts agree that itraconazole penetrates the central nervous system (CNS) poorly (2), perhaps because the efflux brain pumps extrude the drug effectively. Its usefulness in craniocerebral aspergillosis is limited in case reports or small case series that have significant selection (publication) bias. Similarly, some authors report a positive experience with high cumulative doses of amphotericin B deoxycholate. This is a common artificial association and a survival bias in clinical mycology describing patients treated with amphotericin B. Perhaps what would be more interesting is dose intensity of amphotericin B (milligrams per kilogram per day), because conceptually, one needs to give more amphotericin B to clear infections in anatomically difficult sites such as the sinuses or the brain. Other therapeutic options, such as the availability of new antifungals with good CNS penetration, such as liposomal amphotericin B and voriconazole, a potent highly lipophilic orally administered triazole with very good CNS penetration, might change the way we treat craniocerebral aspergillosis in the future.

Finally, exciting developments have occurred with regard to the pathogenesis and diagnosis of neuroaspergillosis. An animal model was recently described (1) that could potentially facilitate the study of therapeutic options in CNS aspergillosis. Also, the secretion of narcotizing factors by *Aspergillus* toward neurons and glial cells has been described (4). New promising developments for the diagnosis of neuroaspergillosis by detection of the *Aspergillus* galactomannan in the cerebrospinal fluid (6) offer promise for a more timely diagnosis of this difficult infection.

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1. Chiller TM, Luque JC, Sobel RA, Farrokhshad K, Clemons KV, Stevens DA: Development of a murine model of cerebral aspergillosis. **J Infect Dis** 186: 574–577, 2002.

2. De Beule K, Van Gestel J: Pharmacology of itraconazole. **Drugs** 61[Suppl 1]:27–37, 2001.
3. Maraqa NF, Gomez MM, Rathore MH, Alvarez AM: Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. **Clin Infect Dis** 35:50–53, 2002.
4. Speth C, Rambach G, Lass-Florl C, Wurzner R, Gasque P, Mohsenipour I, Dierich MP: Culture supernatants of patient-derived aspergillus isolates have toxic and lytic activity towards neurons and glial cells. **FEMS Immunol Med Microbiol** 29:303–313, 2000.
5. Stevens DA, Lee JY: Analysis of compassionate use itraconazole therapy for invasive aspergillosis by the NIAID Mycoses Study Group criteria. **Arch Intern Med** 157:1857–1862, 1997.
6. Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, Gualandi F, Truini M, Bacigalupo A: Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. **J Clin Microbiol** 40:1496–1499, 2002.
7. Wilson M, Denning DW: The commonest life-threatening mold infection: Invasive aspergillosis. **Hosp Update** 19:225–233, 1993.

In this article, the authors report 25 cases of neuroaspergillosis seen at their hospital during a 12-year period. They describe a clinical grading scheme that is matched with anatomic location and invasiveness, and they conclude that extradural neuroaspergillosis is more favorable than intradural neuroaspergillosis. In addition, they recommend preoperative treatment with itraconazole. The authors have made an informative contribution.

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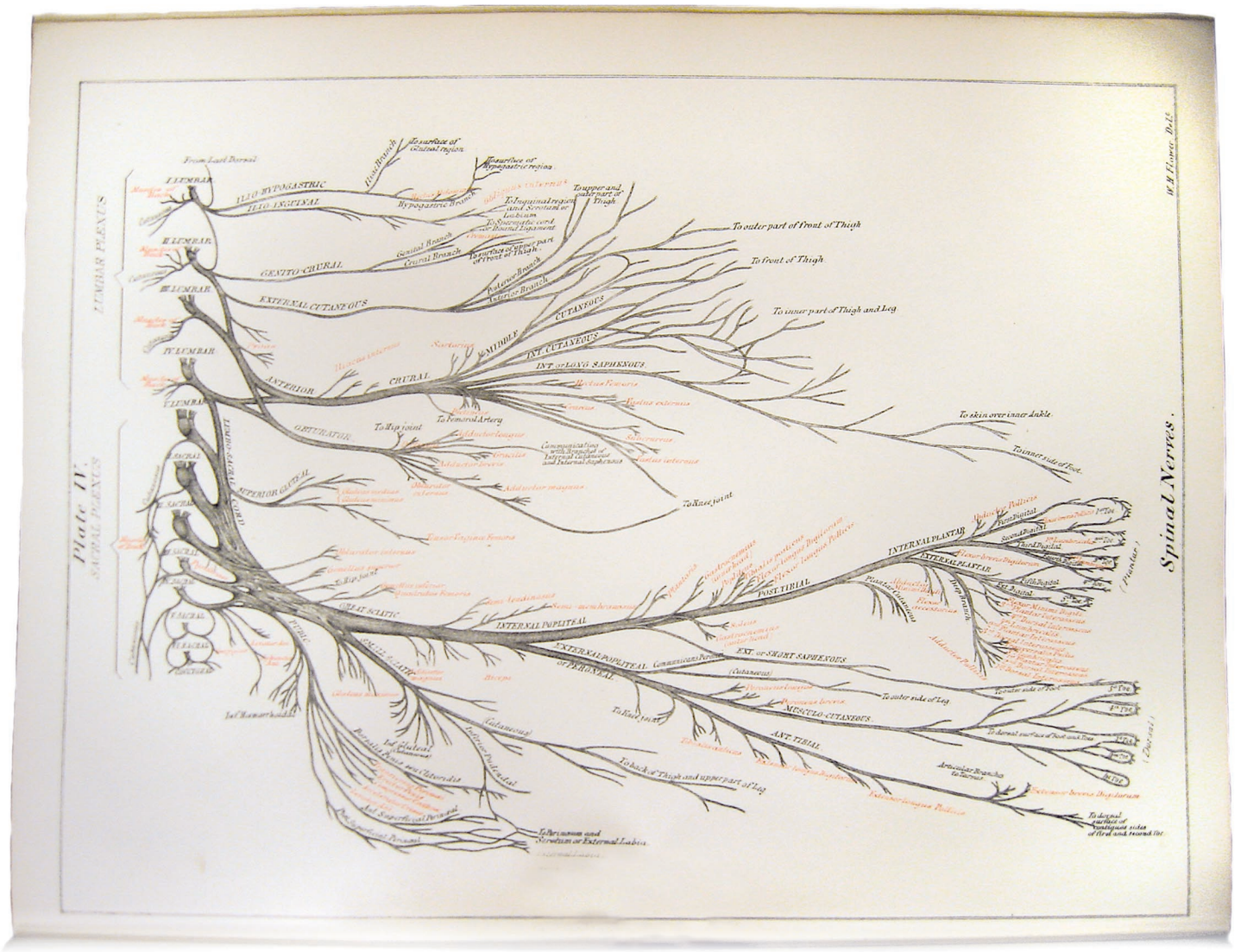

Anatomic plate from William Henry Flower's Diagrams of the Nerves of the Human Body, *published in 1874. Flower (1831–1899), an English biologist, was a leading authority on the arrangement of museums and their exhibits; this is evident in his anatomic drawings in that the nerves appear as if they have been presented in a display case.* *(See page 626 for another plate from Flower.)*