Surgical treatment for fungal infections in the central nervous system

RONALD F. YOUNG, M.D., GEORGE GADE, M.D., AND VERTY GRINNELL, M.D.
Divisions of Neurosurgery and Neuroradiology, University of California, School of Medicine, Harbor/UCLA Medical Center, Los Angeles, California

The hospital records of 78 patients who underwent surgical therapy for fungal infections of the central nervous system (CNS) between 1964 and 1984 are summarized. Nine different fungal types were identified, but Coccidioides immitis and Cryptococcus neoformans accounted for most (67.1%) of the infections. A variety of clinical syndromes were seen, including chronic basal meningitis (45 patients), intracranial mass lesions (12 patients), and communicating hydrocephalus (six patients). Thirteen patients had rhinocerebral forms of fungal infection, and two presented with spinal involvement. Delays in diagnosis were frequent and ranged from 2 months to 11 years. In 31 patients the CNS lesion was the first indication of a fungal infection, and lesion biopsy or cerebrospinal fluid (CSF) examination confirmed the diagnosis. A total of 144 surgical procedures were carried out, including lesion biopsy or excision in 13 patients, primary CSF shunting in 22, and placement of an Ommaya reservoir for administration of intraventricular or intracisternal antifungal agents in 48. All patients received parenteral and, in some cases, intrathecal or oral antifungal chemotherapy in addition to surgical therapy. Overall mortality was 43.6% (34 deaths). With prompt diagnosis and treatment, the mortality rate was 39% whereas, when appropriate treatment was delayed, the mortality rate was 64%. An additional 14 surviving patients (17.9%) exhibited permanent morbidity due to neurological deficits, seizure disorders, or renal toxicity following treatment with amphotericin B. The combined mortality and morbidity rate was 62.8%. Clinical symptoms were resolved completely in 29 patients, although in 10 evidence of disease persisted and chemotherapy was continued. Fungal infections of the CNS are being recognized with increased frequency. It is suggested that a high index of suspicion, aggressive attempts to obtain a diagnosis, and early and vigorous therapy may reduce the unfortunate outcome seen in a relatively high proportion of patients with CNS fungal infections.

Key Words: fungus infection • brain abscess • surgical treatment • meningitis • hydrocephalus

Intracranial fungal infections are being diagnosed more frequently for a variety of reasons, including an increased awareness of such infections, improved techniques for biopsy of intracranial lesions, a larger pool of patients with increased susceptibility to fungal infections because of reduced host defenses, and increased travel to regions where certain fungi are endemic. A large number of individual case reports and small series of patients with fungal infections of the central nervous system (CNS) have appeared in the literature; however, few descriptions of large groups of such patients are available to assist in understanding the associated clinical syndromes and in assessing the effectiveness of therapy. This report describes an experience with the surgical treatment of CNS fungal infections in 78 patients over a period of 20 years. Several of these patients have been described in previous reports.18,32,59,85,89

Summary of Cases

We reviewed the hospital records of 78 patients treated between 1964 and 1984: 76 were seen at the University of California, Los Angeles, affiliated hospitals, one patient was treated at the Upstate Medical Center, Syracuse, New York, and one was seen at St. Joseph's Medical Center in Burbank, California. We were directly involved in the care of 38 of the patients. There were 56 males and 22 females; their mean age was 34.6 years (range newborn to 72 years) at the time their intracranial fungal infection was diagnosed. Table 1 lists the fungal organisms responsible for the infections in these patients. Coccidioides immitis and Cryptococcus neoformans accounted for 67.1% of the infections. In 45 patients (61%) the presence of a systemic or localized fungal infection outside the nervous system was known prior to the onset of neurological symptoms, whereas in 31 patients (39%) the neurolog-
FIG. 1. Computerized tomography scan following intravenous contrast infusion in a patient with basal meningitis due to *Coccidioides immitis*. The basal cisterns are very clearly delineated. An enlarged aqueduct of Sylvius is also noted due to hydrocephalus.

Clinical symptoms represented the first indication of a fungal infection.

In 29 patients (37%) an altered immune response, a break in the skin, or other conditions predisposing to fungal infections were identified. These conditions included diabetes, leukemia, lymphoma, renal transplantation, prolonged use of antibiotics, myelomeningocele, cerebrospinal fluid (CSF) shunts, and intravenous drug abuse. Twenty-two patients, all with coccidioidomycosis, had a history of travel to or residence in the San Joaquin Valley of California. Thus, a total of 51 patients (65%) either had altered immune responses or had contact with an area in which fungal infections were endemic.

**Clinical Presentation**

Forty-seven patients were known to have suffered localized or systemic fungal infections between 1 month and 15 years prior to the onset of symptoms of intracranial disease. Excluding three patients whose CNS symptoms presented 5 to 15 years after their initial diagnosis of a fungal disease, the mean interval between original diagnosis and onset of CNS symptoms was 4 months.

Patients presented with five clinical neurological syndromes, namely: 1) basal meningitis; 2) intracranial mass lesions; 3) hydrocephalus; 4) rhinocerebral involvement; and 5) spinal manifestations. Forty-five patients presented with clinical symptoms and signs of meningitis, including headache, neck stiffness, fever, lethargy, alterations in mental status, and cranial nerve palsies. In contrast to patients with bacterial meningitis, the symptoms in these patients were often mild and gradually progressive over days, weeks, or even months prior to diagnosis. Four fungal types were responsible for the 45 instances of fungal meningitis: *Coccidioides* (26 cases), *Cryptococcus* (14 cases), Candida (four cases), and *Aspergillus* (one case). Three of our patients with fungal meningitis had had CSF shunts placed previously to control hydrocephalus unrelated to fungal infections. These patients had experienced multiple shunt revisions and bacterial shunt infections treated by antibiotic therapy before their fungal infections with *Candida albicans*.

Twelve patients presented with evidence of intracranial mass lesions, single in four patients and multiple in eight. Symptoms and signs included seizures, headaches, alteration in mental status, and focal neurological deficits. Seven fungi were identified as the etiological agents in these 12 patients: *Nocardia* (four cases), *Cryptococcus* (three cases), and one case each of *Rhizopus* (mucormycosis), *Aspergillus*, Blastomyces, *Histoplasma*, and *Drechslera*.

Six patients presented with primary evidence of hydrocephalus, including headaches and alterations in mental function or level of consciousness. Although all patients in this group were ultimately found to have chronic basal meningitis as an underlying cause of their hydrocephalus, their initial clinical presentation did not suggest meningitis. Fever, neck stiffness, and cranial nerve palsies were absent in this group. Radiographic procedures revealed ventriculomegaly and led to a primary diagnosis of idiopathic communicating hydrocephalus in virtually all the patients in whom a prior history of systemic fungal disease was not obtained. Two fungi were responsible for the six cases of primary hydrocephalus: *Coccidioides* in four and *Cryptococcus* in two. Delayed secondary hydrocephalus due to fungal basilar meningitis, requiring CSF shunting, occurred in...
Surgical treatment for CNS fungal infections

an additional 16 patients; 11 cases were caused by Coccidioides and five by Cryptococcus.

Thirteen patients presented with rhinocerebral infections due to either Rhizopus (mucormycosis) or Aspergillus. Symptoms included unilateral proptosis, visual loss, ophthalmoplegia, and loss of facial sensation. A prompt diagnosis was made in these patients, particularly in the presence of known diabetes. Two of these patients eventually developed hemispheric neurological deficits caused by internal carotid occlusion secondary to fungal arteritis.

Two patients presented with purely spinal manifestations of fungal infection. One developed progressive paraparesis secondary to an epidural fungal lesion in the mid-thoracic region. The other presented with neck pain, and radiological studies disclosed a lytic lesion in the C-6 vertebral body. The responsible organisms were Cryptococcus in the first patient and Coccidioides in the second.

In 31 patients, symptoms of neurological disease were the first clinical evidence of a fungal infection. Of this group, 13 had rhinocerebral forms, seven showed evidence of mass lesions, five had meningitis, and six had hydrocephalus.

Diagnosis

Radiology. Computerized tomography (CT) was the most helpful radiological study for diagnosis of the CNS fungal infections, although unfortunately none of the fungi exhibited an absolutely diagnostic CT pattern. Angiography or venography was also helpful in the diagnosis of mucormycosis and Aspergillus infections, which frequently produced arteritis and arterial and/or venous occlusion.

In the patients who presented with a clinical syndrome of meningitis, CT scanning without intravenous contrast enhancement was usually normal. Enhancement of the meninges surrounding the basal cisterns was seen in 50% of those receiving intravenous contrast material (Fig. 1). In patients who presented with the clinical syndrome of hydrocephalus, the CT scan showed diffuse ventriculomegaly. In one patient with hydrocephalus, fourth ventricular obstruction resulting from Cryptococcus infection was revealed in the cerebellum (Fig. 2). Following therapy with resolution of the area of inflammation, the hydrocephalus resolved without shunting.

In the patients with the rhinocerebral form of mucormycosis or aspergillosis, typical changes in the paranasal air sinuses and orbits were seen. These changes included soft tissue-density masses without fluid levels and opacified air cells interspersed with normal cells. Involvement was nearly always unilateral. The majority of patients also had orbital invasion represented by thickening and lateral displacement of both the medial rectus muscle and the optic nerve, and increased density at the orbital apex. Bone destruction was identified in less than half of the cases. Two patients showed major arterial occlusion secondary to fungal arteritis and secondary thrombosis (Fig. 3 upper), with resultant cerebral infarction (Fig. 3 lower). One patient with mucormycosis developed a true "mycotic" aneurysm. Cavernous sinus venography demonstrated orbital venous or cavernous sinus occlusion in four patients. In two patients intracranial masses caused by either mucormycosis or Aspergillus had the typical appearance of an abscess, including a spherical lesion with a capsule and a less dense central region (Fig. 4).

Patients presenting with intracranial mass lesions displayed a variety of CT patterns. The intracranial lesions were either solid granulomas or abscesses and, in either form, presented the CT appearance of nodules or rings which enhanced with intravenous contrast material. Both single and multiple lesions were seen. Associated edema was not always present. In general, the rings of these fungal lesions tended to be more irregular and thicker than the rings of pyogenic abscesses. Less contrast enhancement was seen in immunocompro-
mised patients. Calcium was deposited in some granulomas, making these older lesions hyperdense compared to brain tissue. In our experience, *Cryptococcus* was a common organism producing either single or multiple intracranial mass lesions. These lesions were poorly seen on noncontrast CT scans, and enhanced poorly after administration of intravenous contrast material. Four patients had mass lesions caused by *Nocardia*; multiculated abscesses were seen in three, and in one patient a single granuloma was identified (Fig. 5).

*Histoplasma* and *Blastomyces* produced granulomatous lesions in two patients. The blastomycotic lesion was seen on noncontrast scans and enhanced significantly with administration of contrast material. In the patient who had harbored lesions caused by *Histoplasma* for over 1 year, the lesions were well defined on noncontrast scans and enhanced little after intravenous infusion of contrast medium (Fig. 6). One patient had a purely granulomatous intracranial mass due to an unusual fungus, *Drechslera spicifera*; this lesion was ill-defined on noncontrast CT but enhanced significantly on the postcontrast scans.

**Mycology.** The causative organism was identified in all 78 cases. The 13 patients who underwent biopsy or resection of a mass lesion had histopathological identification of the responsible organism. Of the 51 patients presenting with either meningeal signs or hydrocephalus, the correct diagnosis was established by examination of CSF obtained by lumbar, cisternal, or ventricular puncture. In 26 patients the correct initial diagnosis was established by CSF serological studies, in 13 patients by histological identification of organisms in the CSF, and in 12 by positive CSF cultures. After an initial diagnosis was established by one of these methods, further confirmation of the diagnosis was usually also obtained from one or more of the other tests.

An initial misdiagnosis was made in 14 patients (16%), as follows: idiopathic communicating hydrocephalus (six patients), metastatic carcinoma (two patients), tuberculosis (two patients), and sarcoidosis, bacterial brain abscess, glioma, and cisticercosis (one patient each). Intervals ranging from 2 months to 11 years elapsed in these patients before the correct diagnosis was made. In one patient, initially thought to have a bacterial brain abscess, the misdiagnosis led directly to death. The correct diagnosis of *Nocardia asteroides* abscess was not discovered until ineffective antibiotic therapy was followed by disease progression and trans-tentorial herniation; diagnosis was established at craniotomy when the patient was moribund.

Another patient underwent CSF shunting for treatment of hydrocephalus thought to be due to fourth ventricular outlet obstruction resulting from cisticercosis. The patient deteriorated and died, despite control of the hydrocephalus. Postmortem examination showed severe diffuse meningoencephalitis due to *Coccidioides immitis*. Thus, two patients died as a result of misdiagnosis and inappropriate therapy. In another patient with known cryptococcal meningitis, a secondarily developing intracerebral mass was assumed to be due to recurrent fungal infection. Unsuccessful antifungal chemotherapy without lesion biopsy resulted in the patient’s death, and an autopsy disclosed an atypical intracranial lymphoma.

**Treatment**

All patients received antifungal chemotherapy. Amphotericin B was administered to 74 patients, to 20 by the intravenous route only and to 54 intrathecally and/or intraventricularly via an Ommaya reservoir. Sixteen patients received 5-fluorocytosine either intravenously...
Surgical treatment for CNS fungal infections

### TABLE 1
Clinical syndromes in 78 patients with central nervous system fungal infections

<table>
<thead>
<tr>
<th>Infecting Organisms</th>
<th>Meningitis</th>
<th>Mass Lesion</th>
<th>Hydrocephalus</th>
<th>Rhinocerebral Involvement</th>
<th>Spinal Involvement</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coccidioides immitis</td>
<td>26</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nocardia asteroides</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Rhizopus species (mucormycosis)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drechslera spicifera</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>total cases</td>
<td>45</td>
<td>12</td>
<td>6</td>
<td>13</td>
<td>2</td>
<td>78</td>
</tr>
</tbody>
</table>

or via a combination of intravenous and intrathecal routes. Six patients also received intravenous and/or intrathecal miconazole and four received oral ketoconazole. The four patients with Nocardia infections were treated with sulfisoxazole, trimethoprim, ampicillin, and erythromycin. Fifty-four patients received intrathecal antifungal agents given by repeated lumbar, cisternal, or lateral cervical punctures and, in 48 of these patients, either intraventricular or intracisternal antifungal agents were also given via an implanted Ommaya reservoir.

A total of 144 surgical procedures were performed in these 78 patients (Table 2). Eighty-three of these were primary procedures for biopsy or excision of mass lesions and placement of CSF shunts or Ommaya reservoirs. Secondary procedures were performed to correct complications of shunts (21 cases) or Ommaya reservoirs (10 cases), or to electively remove Ommaya reservoirs (seven cases). Seventeen of 48 patients with Ommaya reservoirs (35.4%) experienced 23 complications, including 10 catheter obstructions, seven infections, one inadvertent lodgement of the catheter tip in brain tissue, four seizures, and one intracerebral hematoma. Twenty-two patients underwent CSF shunting, including six who originally presented with signs and symptoms of hydrocephalus and 16 who originally presented with meningitis but who subsequently developed hydrocephalus despite chemotherapy. A total of 21 revisions were required in 12 of these patients for treatment of shunt-related complications, most of which were peculiar to patients with fungal infections. Of nine patients presenting with shunt obstructions, seven showed evidence of fungal growth causing the obstruction within the distal shunt catheter. In addition, four patients developed subcutaneous fungal growth along the distal catheter track, which in three cases eventually drained through the skin. Three patients in whom CSF shunts had originally been placed for treatment of nonfungal hydrocephalus (due to aqueductal stenosis in two and Arnold-Chiari malformation in one) were subsequently treated for Candida albicans ven-

### TABLE 2
Surgical procedures in 78 patients with CNS fungal infections

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ommaya reservoir placement</td>
<td>48</td>
</tr>
<tr>
<td>Ommaya reservoir revision</td>
<td>10</td>
</tr>
<tr>
<td>Ommaya reservoir removal</td>
<td>7</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>22</td>
</tr>
<tr>
<td>CSF shunt revision</td>
<td>21</td>
</tr>
<tr>
<td>lesion biopsy or excision</td>
<td>13</td>
</tr>
<tr>
<td>sinus-orbit exenteration</td>
<td>13</td>
</tr>
<tr>
<td>ventriculostomy</td>
<td>6</td>
</tr>
<tr>
<td>bacterial abscess drainage</td>
<td>1</td>
</tr>
<tr>
<td>anterior vertebral resection</td>
<td>1</td>
</tr>
<tr>
<td>laminectomy</td>
<td>1</td>
</tr>
<tr>
<td>clipping of aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>total procedures</td>
<td>144</td>
</tr>
</tbody>
</table>

* CNS = central nervous system; CSF = cerebrospinal fluid.
triculitis, meningitis, and shunt infection requiring seven shunt revisions.

Results of Treatment

Of the 78 patients, 34 (43.6%) died. In 24 patients, death was a direct result of uncontrolled CNS fungal infections. Four patients died of causes other than their fungal infections (one from a pulmonary embolus, two from an intracerebral hemorrhage after shunt or reservoir revision, and one from an intracranial lymphoma). Autopsy in each of these four patients disclosed active fungal infections. One patient died of a spontaneous intracerebral hematoma without evidence of active fungal disease. In 14 patients in whom diagnostic delays ranging from 2 months to 11 years preceded appropriate therapy, there were nine deaths (64%), whereas there were 25 deaths (39%) among the remaining 64 patients. The mean length of survival in the 17 patients who died was 27 months (range 1 week to 8 years). Fifteen surviving patients (19.2%) suffered permanent morbidity, including blindness, seizure disorders, cranial nerve palsies, and focal or generalized neurological deficits and renal dysfunction (the latter related to amphotericin B therapy). Thus, the combined mortality and permanent morbidity rate was 62.8%. The 44 surviving patients were followed for periods from 8 months to 19 years (mean 8.6 years). At the time of last follow-up review, 14 patients were still receiving various forms of antifungal chemotherapy for treatment of persistent disease. Thus, only 30 patients (38.5%) could be considered cured of their fungal infections.

Table 3 relates the mortality rate to the responsible fungus. Fairly good results were achieved after treatment of Candida, Coccioidioides, and Cryptococcus infections, and mucormycosis. Poor results were obtained with therapy of Aspergillus and Nocardia infections. As only one patient each had Blastomyces, Histoplasma, and Drechslera, conclusions as to outcome would be meaningless.

In Table 4 the mortality rate is analyzed in relation to the type of clinical presentation. No striking differences were observed among the intracranial forms of fungal infection. The mortality rate ranged from 42%

Table 4

Mortality rate according to clinical syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Alive</th>
<th>Dead</th>
<th>Total Cases</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>meningitis</td>
<td>25</td>
<td>20</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>mass lesion</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>rhinocerebral involvement</td>
<td>7</td>
<td>6</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>spinal involvement</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>total cases</td>
<td>44</td>
<td>34</td>
<td>78</td>
<td>43.6</td>
</tr>
</tbody>
</table>

for mass lesions to 50% for hydrocephalus. It is worth noting that both patients with spinal disease survived.

Discussion

Fungal infections of the CNS are being recognized with increasing frequency. Fungi, in general, are ubiquitous organisms with low virulence, although certain fungi, such as *Coccioidioides immitis*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum*, may cause disease in humans with apparently normal host defenses. Infections by these organisms are usually pulmonary in origin and occur most often in endemic regions, such as the southwestern United States (Arizona) or the San Joaquin Valley in California. Localized outbreaks of these pathogenic fungi have been recorded in other geographic regions, and spontaneous cases also occur. Epidemiological studies indicate that, while attack rates for coccidioidal infection are little influenced by race, the rate of dissemination of the disease is 175 times higher for individuals of Filipino ancestry and 10 to 20 times higher for blacks than for Caucasians. Some recent studies suggest that careful evaluation of patients with apparently normal host defenses who contract fungal infections will demonstrably affect certain immune functions.

Another group of fungi, including *Aspergillus* species, *Candida albicans*, *Nocardia asteroides*, and members of the *Zygomycetes* class (mucormycosis), are opportunistic organisms which usually cause infections only in hosts with compromised defenses, such as in the newborn, in patients receiving immunosuppressive drugs, in renal, cardiac, or other transplant patients, or in patients with malignancies. The prolonged use of antibiotics or corticosteroids and chronic breaks in the skin, such as occur with burns, intravenous drug abuse, intravenous hyperalimentation, or use of intravenous catheters in general, also alter host defenses. Other disease states, such as diabetes mellitus, the use of radiotherapy, and the presence of implanted foreign bodies are associated with reduced host defenses and an increased incidence of systemic and CNS fungal infections. One or more of these risk factors was identified in 37% of our patients, and another 28% resided in or near geographic zones in which the fungi are endemic. We could not identify any predisposing factor in 35% of patients. The high incidence of coccidioidal infections in our population is certainly related to the location of our hospitals in the
Surgical treatment for CNS fungal infections

Southwestern United States, in close proximity to the San Joaquin Valley and Arizona. Previous studies have suggested Cryptococcus neoformans as the commonest fungus producing intracranial infection, but recent autopsy series indicate that Candida species may be more common. The presence of the risk factors described should lead to a high index of suspicion of a possible fungal etiology when patients present with CNS disease of unknown etiology. The usual route of CNS fungal infection is thought to be hematogenous, and occasionally true “mycotic” aneurysms caused by fungal endarteritis have been reported. Members of the Aspergillus species and the Zygomyetes class (mucormycosis) commonly produce infections in the paranasal air sinuses and orbit contiguous with the intracranial compartment, and enter the brain by direct extension. These fungi also frequently cause occlusion of major arteries to the brain, such as occurred in two patients in this series, resulting in secondary cerebral infarction.

The clinical symptom complexes that we have noted are encountered frequently by neurosurgeons and deserve careful consideration. Misdiagnoses and delayed diagnoses have been common in our patient population and in literature reports. Problems in diagnosis are encountered for two main reasons: 1) failure to consider a possible fungal etiology, and 2) failure to aggressively pursue a tissue or laboratory diagnosis. Avoidable treatment delays for as long as 1 year or more occurred in 16% of our patients, and at least three deaths occurred because the misdiagnosis was not discovered until the patient was moribund or until postmortem examination.

Chronic meningitis with lethargy, headache, and neck pain of gradual onset and slow progression was the symptom complex we saw most commonly. Coccioidioides, Cryptococcus, Candida, and Aspergillus accounted for all of the meningitis cases in this series. The syndrome of fungal meningitis has been described extensively in the literature. Coccioidioides immitis, Cryptococcus neoformans, and Candida albicans are the organisms most frequently responsible. Although Blastomyces has also been described as producing meningitis, we have not seen a single such case in 20 years. Stockstill and Kauffman recently compared the CSF findings in patients with cryptococcal and tuberculous meningitis and concluded that the two diseases could not be separated on the basis of routine CSF findings alone. Both forms of meningitis demonstrated an elevated white blood cell count (mean 116 to 130 cells/µl), a predominance of lymphocytes (mean 60% to 70%), elevated protein levels (mean 211 to 247 mg/100 ml), and reduced glucose content (mean ratio to serum glucose 0.3 to 0.4:1).

Specific fungal studies are essential to confirm a diagnosis of fungal meningitis. These include cytological examination, culture, and serology. Cytological examination, particularly utilizing the India ink stain, is very useful for diagnosis of Cryptococcus neoformans. Cultures for fungus identification are important, but attention must be given to using proper growth media and to retaining cultures for long periods (up to 8 weeks) because of the fastidious nutritional requirements and slow growth of most fungi. It is essential to notify the bacteriological laboratory staff that fungal organisms are being sought.

Serological tests of CSF are also very useful, although indirect, methods for diagnosis of CNS fungal infections. Serological methods can identify CNS infection caused by Coccioidioides and Cryptococcus in a high percentage of cases, and also by Histoplasma and perhaps Candida and Rhizopus (mucormycosis) in a smaller percentage. Unfortunately, serological tests for Blastomyces, Aspergillus, and Nocardia are of little or no value.

Thirteen patients presented with rhinocerebral forms of fungal infections. The rhinocerebral form occurs exclusively with members of the Aspergillus and Rhizopus species. Infections with the latter group of organisms are commonly referred to as “mucormycosis” or “phycomycosis,” but the general term “zygomycosis” is more appropriate since members of the genus Rhizopus are all Zygozymyces. Such infections originate in the paranasal air sinuses and extend to the orbits or directly intracranially. Both arterial and venous occlusions with secondary cerebral infarction are common. The most common predisposing factor for the zygomycotic form of rhinocerebral infection is diabetic ketoacidosis.

Misdiagnosis was uncommon in our patients with rhinocerebral disease, particularly in the eight patients with diabetes. The onset of proptosis, reduced vision, cranial nerve palsies, and abnormalities in the paranasal air sinuses on radiographic studies nearly always leads to an early biopsy confirming the correct diagnosis. Cure rates from 50% to 89% have been reported when infection is confined to the extracerebral areas only; however, survival with associated brain abscess is rare. Our overall survival rate for rhinocerebral infection with Aspergillus or Rhizopus was 54% after treatment with a combination of radical surgical resection of the infected extracerebral tissues, drainage of intracranial abscesses, and aggressive antifungal chemotherapy.

In the 12 patients with mass lesions and the six presenting with signs and symptoms of hydrocephalus, misdiagnosis was common. In all, 14 of these 18 patients were initially misdiagnosed, and in three death was directly attributable to this misdiagnosis because appropriate therapy was never given or was given only when the patient was moribund. In the other 11 patients, intervals ranging from 2 months to 11 years elapsed until the correct diagnosis was made. The importance of the delay in diagnosis is demonstrated by the mortality rate of 64% in patients in whom a delay was identified compared to 39% in those diagnosed without undue delay. Others have also noted the importance of early diagnosis to successful therapy.

The incidence of misdiagnosis of patients presenting...
with hydrocephalus of undetermined origin can be reduced if a high index of suspicion is maintained for a possible fungal etiology. If lumbar puncture can be safely carried out, the CSF obtained may be diagnostic. Negative lumbar CSF studies, however, do not rule out a fungal etiology for hydrocephalus. Lumbar CSF may be nondiagnostic if CSF flow dynamics are complicated by basal meningitis. In such cases only very large volumes of lumbar CSF or cisternal or ventricular CSF may confirm the diagnosis of fungal infection. Inappropriate therapy (including, in some cases, unnecessary CSF shunting) may occur when hydrocephalus due to fungal meningitis is misdiagnosed. In addition, CSF fungal infections may disseminate into the peritoneal cavity when unsuspected and untreated fungal meningitis presenting as hydrocephalus is treated by CSF shunting. In the face of hydrocephalus of uncertain etiology, careful study of CSF obtained at lumbar or preferably cisternal or lateral cervical puncture is recommended. If a specific diagnosis is not made, we recommend careful histological and serological study for the presence of fungi and culture of ventricular fluid removed at the time of CSF shunt placement.

In the 12 patients with intracranial mass lesions, the symptoms were focal neurological deficits, seizures, or raised intracranial pressure. Misdiagnosis was common and included metastatic carcinoma, tuberculosis, bacterial brain abscess, primary brain tumor, sarcoidosis, and cysticercosis. We believe the incidence of such misdiagnoses can be reduced. Modern neurosurgical techniques allow safe biopsy of lesions in almost any intracranial location. In addition, the recent development of special stains for identification of certain fungi should help reduce the incidence of histopathological misdiagnosis. We believe that attempts to treat undiagnosed intracranial mass lesions without a tissue diagnosis are hazardous. We do not agree with recent recommendations to treat brain abscesses, for instance, without at least aspiration to obtain a bacteriological diagnosis. One of our patients with Nocardia abscess died because aspiration was not carried out until transventricular herniation occurred; this patient had been unsuccessfully treated for a presumed bacterial abscess with broad-spectrum antibiotics which did not include the sulfa compounds useful in treating Nocardia infections. In patients with known systemic Nocardia infections, successful therapy of presumed, but pathologically unproven, intracranial fungal masses with chemotherapy alone has been reported. Although we have occasionally used this approach, it is not without hazard. This was demonstrated by our patient with cryptococcal meningitis who was found at autopsy to have a fatal intracranial mass lesion caused by lymphoma and not by Cryptococcus infection. Lipton, et al., recently suggested that brain biopsy and tissue culture was the most reliable method for diagnosis of intracerebral fungal infections; however, if CSF can be safely obtained, cytological and serological examination may also prove diagnostic.

Spinal infections have been reported due to a number of fungal agents. We have had experience with only two patients with primary spinal fungal infections, one with coccidioidomycosis and one with cryptococcosis. Three other patients who originally presented with meningitis developed secondary spinal complications. As with our two patients, both vertebral osteomyelitis and/or epidural infections causing spinal cord compression have been described. Spinal cord decompression and antifungal chemotherapy are usually successful in resolving the myelopathy, but persistent disability and chronic disease are not uncommon.

The most useful radiographic method for diagnosis of CNS fungal infections is CT scanning, but unfortunately only the rhinocerebral forms of zygomycosis and aspergillosis produce reasonably typical changes, involving the paranasal air sinuses and orbits. Scans of patients with meningitis may be normal or show contrast enhancement of the meninges specific only for a basilar meningitis of any etiology. Likewise, the CT appearance of hydrocephalus secondary to fungal infection is nonspecific. The CT picture of fungal mass lesions varies, and may be confused with primary tumors, bacterial abscesses, and other granulomatous masses. Angiography and orbital venography are extremely useful for diagnosis of the arterial and venous occlusions that occur in cases of aspergillosis and mucormycosis.

Surgery is a very important aspect of the treatment of CNS fungal infections. Surgical procedures may be useful to obtain appropriate tissue or CSF specimens for correct diagnosis of suspected CNS fungal infections. In addition to its role in diagnosis, surgical resection of mass lesions may be therapeutic by reducing mass effect and improving the efficacy of drug treatment. Sometimes, this is life-saving. Placement of an Ommaya reservoir to allow easier intrathecal administration of most antifungal agents is another role of surgery in patients with these infections. The catheter may be placed either intraventricularly or, in the case of fourth ventricular outflow obstruction, intracisternally. We placed both a cisternal Ommaya reservoir and a CSF shunt in 17 of our patients with good results. Complications were seen in 35.4% of our patients who received an Ommaya reservoir; the literature suggests that problems, including reservoir obstruction, lodgement of the catheter tip in the brain, reservoir infection, and seizures, occur in from 11% to 33% of patients with implanted reservoirs. Another frequently beneficial surgical treatment in patients with basilar meningitis and hydrocephalus due to fungal infection is CSF shunting; however, CSF shunts carry many of the same risks as the Ommaya reservoir as well as the additional risk of introducing the fungal organism intraperitoneally. We saw unusually high rates of shunt obstruction due to fungal organisms and instances of fungal wound breakdown along shunt catheter tracks. Others have also...
Surgical treatment for CNS fungal infections

noted this problem with CSF shunts in patients with fungal infections.22

The mainstay of therapy for intracranial fungal infections in the past has been amphotericin B.8,10,25,28,32,36,63,49,52,53,59,74,80,85–87,89,90 This agent can be administered only intravascularly or intrathecally, and is associated with significant systemic and nervous system toxicity. Intravenous administration unfortunately results in low CSF and brain levels of the drug, but this route has been suggested as initial therapy in all susceptible fungal infections, except coccidioidomycosis where combined intravenous and intrathecal therapy is generally recommended.74 Efficacy of this drug in other fungal infections has been shown, but relapses are common10 and the mortality rate remains high. Exact indications for use of intrathecal amphotericin B are controversial, and some authors still consider that the value of intrathecal administration remains unproven.53 Toxic complications of intrathecal therapy, including arachnoiditis with back and leg pain and paraparesis, myelopathy,15 and cranial nerve palsies, have limited its use by this route. Unfortunately, intracranial fungal infections may recur after intravenous treatment alone, even in fungi with the greatest susceptibility to amphotericin B.59

The fluorinated pyrimidine, 5-fluorocytosine, is a newer antifungal agent which, given intravenously or intrathecally, achieves good concentrations in CSF.8,79 It has been shown to be effective against Cryptococcus neoformans, Candida, and Aspergillus infections.68 It is generally given in combination with amphotericin B, since a synergistic action has been demonstrated for the two agents.19 Recently, imidazole derivatives, such as miconazole82 and ketoconazole,11,16,21,23,27 have been utilized for treatment of CNS fungal infections with some success, but persistent disease and recurrences have been reported.65 Miconazole may be given intravenously or intrathecally, whereas ketoconazole is given only orally.8 A completely new group of antifungal agents, the allylamines, has recently been described.65 These compounds appear most effective against the dermatophytes in vitro, but excellent results against Candida and Aspergillus species have been shown.65 Clinical experience with these agents is so far very limited.

Of the fungal organisms commonly producing CNS infections, only Nocardia asteroides is not treated with the antifungal agents described. Although the Nocardia species are commonly considered fungi, there has been considerable discussion of their proper classification.51 These organisms possess certain characteristics of bacteria and other characteristics of fungi.31 The clinical diseases produced by Nocardia, however, closely resemble the disease produced by other "true" fungi.29 A combination of sulfamethoxazole and trimethoprim is recommended for therapy of CNS infections with Nocardia species,71 but failure is not uncommon.67,73 Smego, et al.70 demonstrated cure or improvement in 80% of patients with Nocardia infections, but this rate dropped to 57% when CNS infection was present. Sensitivity of Nocardia species to other antibiotics, including ampicillin, erythromycin, and the aminoglycosides and cephalosporins, has also been reported.81 Kirmani, et al.,47 and Viroslav and Williams60 reported the apparent cure with chemotherapy alone of a patient with what appeared to be multiple Nocardia brain abscesses. Byrne, et al.,14 reviewed the cases of 16 patients reported in the literature to have survived cerebral nocardiosis, including three of their own, and suggested that a combination of chemotherapy and surgical biopsy or excision was the best course of therapy.

Conclusions

Several important conclusions can be drawn from our data.

1. In patients with basal meningitis, fungal infection should be suspected, and appropriate CSF studies carried out.

2. In patients with undiagnosed communicating hydrocephalus, fungal studies of the CSF should be carried out prior to shunting if possible, or alternatively at the time of CSF shunting.

3. When recurrent bacterial CSF shunt infections occur with antibiotic therapy, fungal studies should be performed to rule out possible Candida albicans meningitis.

4. Therapy of undiagnosed intracranial mass lesions is hazardous. Biopsy and appropriate histopathological, bacterial, and fungal studies should be carried out prior to therapy.

5. Early diagnosis, aggressive surgical procedures, and chemotherapy of CNS fungal infections reduced the mortality rate from 64% to 39% in our series.

Acknowledgments

We are grateful to Drs. Herbert Lourie of Syracuse, New York, and Pablo Lawner of Burbank, California, for permission to include patients under their care, and to Dr. Steven Cobb for providing radiological studies of one patient. We thank Lucia Miller and Karen Einstein for assistance with data collection and manuscript preparation.

References


J. Neurosurg. / Volume 63 / September, 1985 379


R. F. Young, G. Gade and V. Grinnell
Surgical treatment for CNS fungal infections


60. Ommaya AK: Subcutaneous reservoir and pump for sterile access to ventricular cerebrospinal fluid. Lancet 2:983–984, 1963


Manuscript received December 17, 1984.

Address reprint requests to: Ronald F. Young, M.D., University of California, Los Angeles, School of Medicine, Harbor/UCLA Medical Center, Box 173, 1000 West Carson Street, Torrance, California 90509.