Neuroimaging as a Guide to Predict Outcomes for Patients with Coccidioidal Meningitis

Edward L. Arsura, 1,2 Royce Johnson, 1 James Penrose, 1 Kenneth Stewart, 2 William Kilgore, 3 Chakradhar M. Reddy, 2 and Ravi K. Bobba 7

1 Department of Medicine, Kern Medical Center, University of California School of Medicine, Bakersfield, and University of Virginia School of Medicine, Roanoke-Salem Program

Sixty-two patients with coccidioidal meningitis underwent neuroimaging. Magnetic resonance imaging detected neuroimaging abnormalities in 76% of patients, and computed tomography scanning detected neuroimaging abnormalities in 41.6%. The most common abnormal neuroimaging findings were hydrocephalus (51.6%), basilar meningitis (46.8%), and cerebral infarction (38.7%). Significantly elevated mortality rates were associated with hydrocephalus and hydrocephalus coexisting with infarction. Basilar meningitis did not influence outcome. Patients without neuroimaging abnormalities had a mortality rate of 7.7%.

The pathogenic fungus Coccidioides immitis causes coccidioidomycosis. The organism is found in the soil of areas where it is endemic, which include vast stretches of the American Southwest. Approximately 60% of individuals exposed to C. immitis are asymptomatic or demonstrate mild illness. The remaining 40% develop predominantly self-limited pulmonary symptoms [1]. Disseminated disease may develop in ≤5% of symptomatic patients [2] and is associated with significant morbidity and, occasionally, mortality.

Dissemination to the meninges is one of the most devastating complications of coccidioidomycosis. Coccidioidal meningitis is associated with increased mortality, and the course of therapy for survivors may be prolonged and difficult to endure.

The most important abnormal neuroradiologic findings (hereafter, neuroimaging abnormalities) for patients with coccidioidal meningitis are hydrocephalus, basilar meningitis, and cerebral infarction. Mass lesions, hemorrhage, and calcification are seen less frequently [3, 4]. In this report, we describe the neuroimaging abnormalities detected in a large cohort of patients with coccidioidal meningitis, and we demonstrate that neuroimaging can assist in determining prognosis. We also compare the frequency that neuroimaging abnormalities were detected by CT scanning and by MRI.

**Methods.** The study population included all patients with coccidioidal meningitis who were treated at Kern Medical Center (KMC) from 1991 to 1997. KMC is located in California’s Central Valley, an area where coccidioidomycosis is endemic.

Coccidioidomycosis was diagnosed in patients who had a compatible illness accompanied by coccidioidal serologic test results. Coccidioidal serologic test results were considered positive if the complement fixation titer was ≥1:4. Coccidioidal meningitis was diagnosed if characteristic symptoms and lymphocytic pleocytosis were present. CSF samples from 52 patients yielded positive complement fixation titers. The Kern County Public Health Department performed all serologic testing. Microscopic confirmation of infection was done using Gomori methenamine silver stain modified for C. immitis. The organism was cultured using standard microbiologic methods.

Neuroimaging was performed as part of the evaluation of all patients with suspected coccidioidal meningitis and also for patients with known or suspected meningitis that manifested an important change in the course of illness. Neuroimaging was performed, with and without contrast, using a General Electric 9800 CT Scanner and/or a General Electric 1.5 Tesla closed MRI. Iodinated contrast was used for CT scans, and gadolinium for MRI studies. The KMC Institutional Review Board approved this study. Pertinent data were abstracted and entered into a database. Information for this study was synthesized from the database and from retrospective chart reviews.

Staff radiologists at KMC, who were intimately knowledgeable about coccidioidal meningitis, reviewed radiological studies. Neuroimaging abnormalities of interest were hydrocephalus, basilar meningitis, and cerebral infarction. The radiological diagnosis of hydrocephalus was made on the basis of the presence of dilatation of the bodies of lateral ventricles, rounding and enlargement of the frontal horns, and an increase in size and rounding of the temporal horns without associated generalized atrophy of cerebral tissue. Basilar meningitis indicates abnormal leptomeningeal enhancement in the area of the basal cisterns; the radiological diagnosis was made on the basis of abnormal leptomeningeal enhancement visible
on contrast-enhanced CT scans or MRIs. Cerebral infarction was diagnosed on the basis of time-dependent findings from either CT scanning or MRI. Diagnostic findings of CT scans performed early in the course of illness included hypodensity and asymmetry of the sulci from one hemisphere to the other and changes in distinction between the density of gray and white matter. Findings of CT scans performed later in the course of the illness included focal attenuation and progressive localized mass effect. More chronic disease was defined by presence of a well-defined focal lucency.

Patients were followed-up for a minimum of 12 months or until death. Demographic characteristics and presence of factors commonly associated with a greater likelihood of dissemination were assessed. The main outcomes were mortality and the determination of an association between mortality and the presence of neuroimaging abnormalities. We also compared the frequency that abnormalities were detected by CT scanning and by MRI.

Statistical analyses were performed using SPSS, version 11.0 for Windows (SPSS). Means are presented as means ± SDs. Mortality rates for each group of patients with coccidioidal meningitis and single or multiple neuroimaging abnormalities were compared with the mortality rate for individuals without neuroimaging abnormalities (the control group). Results are reported as absolute, relative, and attributable risks. The absolute risk reflects the probability of death in each group with neuroimaging abnormalities; the relative risk indicates the fold-increase in the frequency of the outcome, compared with that of the control group; and the attributable risk defines the prevalence of the outcome primarily attributed to the independent variable (i.e., neuroimaging findings). The difference in categorical variables, including mortality rates, between patient groups with single or multiple neuroimaging abnormalities and patients without abnormalities, was assessed using the $\chi^2$ test. The difference between mean values for patients without neuroimaging abnormalities and groups with abnormalities was tested using the independent $t$ test.

**Results.** Sixty-three patients entered the study. Their mean age was 35 ± 13 years. Forty-six patients were male, and 17 were female. One patient was excluded because pertinent information was unobtainable. Of the 62 patients, 33 were Hispanic, 11 were African-American, 11 were white, 5 were Filipino, and 2 were Asian. Two patients were infected with HIV, 3 were pregnant, 1 was post-partum, 9 had diabetes, 22 smoked tobacco, 15 were alcohol abusers, 4 were injection drug users, and 3 abused other illicit substances. Eight patients were lost to follow-up; their clinical characteristics and results from neuroimaging studies are included in our analysis, but their data were excluded in determination of the mortality rate.

The control group was similar to the groups with neuroimaging abnormalities: no significant differences were detected with respect to ethnicity; sex; concomitant chronic disease; or sites of dissemination, including the meninges (predominantly skin and bone). The mean age of patients in the control group was significantly less than that of patients in the groups with abnormalities (28.1 ± 10.3 years vs. 37.1 ± 12.6 years; $P<.05$). With regard to mortality rates, this difference should favor the group with neuroimaging abnormalities. Patients with and without neuroimaging abnormalities did not differ with respect to antifungal therapy received: 44 patients received fluconazole (400–800 mg per day), 4 received fluconazole and amphotericin intrathecally, 4 received amphotericin followed by fluconazole, 4 received amphotericin intravenously, 1 received amphotericin intrathecally and intravenously, and 5 received amphotericin followed by fluconazole intravenously and intrathecally.

The frequencies of hydrocephalus, basilar meningitis, cerebral infarction, and the combinations of these conditions is shown in table 1. Forty-five patients (72.5%) had at least 1 of these abnormalities. Thirty-two patients (51.6%) had hydrocephalus. Twenty-nine patients (46.8%) had basilar meningitis. Twenty-four patients (38.7%) had cerebral infarction. Multiple neuroimaging abnormalities were frequent.

Thirty-six patients (58%) underwent CT scanning and MRI; 14 (22.6%) patients only underwent MRI; and 12 patients (19.4%) only underwent CT scanning. Findings of MRI were abnormal for 38 (76%) of 50 patients, and findings of CT scanning were abnormal for 20 (41.6%) of 48 patients. Both types of imaging showed abnormalities in 12 patients (33%). Seventeen patients (27%) had no neuroimaging abnormalities. No patient had neuroimaging abnormalities detected by CT scanning that were not also detected by MRI. MRI detected neuroimaging abnormalities in 16 patients that were not detected by CT scanning (6 patients with basilar meningitis, 6 patients with basilar meningitis and infarction, and 4 patients with cerebral infarction).

Of 54 patients who completed the study, the 13 patients without neuroimaging abnormalities had a mortality rate of 7.7% ($n = 1$). The mortality rate of this control group was significantly lower than the mortality rate of 31.7% ($n = 13$) for patients with neuroimaging abnormalities ($P<.01$). Further analysis of the various subgroups revealed that the difference in mortality rate was accounted for by the difference in mortality rate between the control group and the groups with hydrocephalus ($P<.03$) and with hydrocephalus and cerebral infarction ($P<.02$).

There was a 12.5-fold increased mortality rate among patients with hydrocephalus and an 11.8-fold increased mortality rate among patients with hydrocephalus and cerebral infarction, compared with the mortality rate among patients without neuroimaging abnormalities. Basilar meningitis was not associated with an increased mortality rate.

**Discussion.** This article focuses on the association of neu-
roimaging abnormalities with mortality and assesses the frequency of neuroimaging abnormalities among patients with coccidioidal meningitis.

The overall mortality rate for patients in our series was 26% (14 of 54 patients), a rate similar to other series of patients with coccidioidal meningitis. Hydrocephalus was the most frequent complication, occurring in 32 (51.6%) patients. The group with hydrocephalus (encompassing patients with hydrocephalus, hydrocephalus and meningitis, hydrocephalus and infarction, or all 3 abnormalities) had a mortality rate of 38.7%. Hydrocephalus alone and hydrocephalus and infarction were frequent and were associated with the highest mortality rate. The explanation for the increased mortality rate among patients with hydrocephalus is unclear. Potentially, the rise in intracranial pressure can lead to neuronal damage, or possibly the inflammatory response in patients with hydrocephalus is more extensive or pronounced.

Our study is unique because we compared the frequency that findings were detected by MRI and/or CT scanning. Previous studies have used only 1 method of imaging [3, 5, 6]. Findings of MRI were positive for 76% of the patients, and findings of CT scanning were positive for 41.6%. There are, however, limitations to our study. Many factors influence mortality rates among people with coccidioidal meningitis, and we did not account for all variables. For example, age, ethnicity [7, 8], and immunologic status [9–11] affect outcome in people with coccidioidal meningitis. The mortality rate is higher with widely disseminated disease [12] than it is with isolated meningeal involvement. Also, our population is somewhat transient, and 8 patients were lost to follow-up. Despite these shortcomings, we believe that the data presented will be useful to clinicians who manage patients with coccidioidal meningitis.

In conclusion, neuroradiological examination can assist the clinician in determining the outcome of coccidioidal meningitis. Patients with hydrocephalus or hydrocephalus and infarction had the highest mortality rate. Patients without these neuroimaging abnormalities had a much lower mortality rate. MRI is superior to CT scanning for detecting neuroimaging abnormalities in patients.

---

**Table 1. Frequency of neuroimaging abnormalities and mortality among patients with coccidioidal meningitis.**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. of patients (% of total)</th>
<th>Patients included in studya</th>
<th>No. included/ no. who died</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32 (51.6)</td>
<td>31/12</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>Only hydrocephalus</td>
<td>4 (6.5)</td>
<td>4/3</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus and basilar meningitis</td>
<td>10 (16.0)</td>
<td>10/1</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus and cerebral infarction</td>
<td>7 (11.3)</td>
<td>7/5</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>Basilar meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (46.8)</td>
<td>26/4</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Only basilar meningitis</td>
<td>7 (11.3)</td>
<td>5/0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Basilar meningitis and cerebral infarction</td>
<td>1 (1.6)</td>
<td>1/0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24 (38.7)</td>
<td>22/9</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Only cerebral infarction</td>
<td>5 (8.1)</td>
<td>4/1</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus, basilar meningitis, and cerebral infarction</td>
<td>11 (17.7)</td>
<td>10/3</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>No abnormalities</td>
<td>17 (27.4)</td>
<td>13/1</td>
<td>7.7</td>
<td></td>
</tr>
</tbody>
</table>

a Patients with neuroimaging abnormalities after exclusion of patients lost to follow-up.

---

Acknowledgment

**Potential conflicts of interest.** All authors: no conflicts.

References