Coccidioidal Meningitis in Kings County
A Public Health Perspective

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Introduction

“It is particularly important to recognize the development of coccidioidal meningitis early and the possibility must be kept in mind when the illness of primary infection persists. The physician should not hesitate to do a lumbar puncture and examination of the spinal fluid if there is headache, prolonger fever or other suggestive symptoms.” [1]

Writing almost a half century ago, William Winn, M.D., a pioneer in the treatment of coccidioidal meningitis, noted the critical role of cerebral spinal fluid (CSF) examination in the management of patients with coccidioidal meningitis (CM). As will be discussed, the examination of CSF remains the optimal means of diagnosing CM before the onset of complications associated with both increased morbidity and mortality. The safety of CM treatment has improved greatly in the last fifty years. The condition remains incurable and usually requires lifetime treatment. A community based approach to CM may facilitate the earlier diagnosis and appropriate, on-going treatment of meningitis due to coccidioidomycosis.

Kings County, California

Located in the southwestern San Joaquin Valley, Kings County is endemic for coccidioidomycosis with an observed incidence rate exceeded in California only by neighboring Kern County. For the period 2001-2008 the rate in Kings County was 70.6/100,000, about half the rate observed in Kern County. [2] The population of Kings County is 152,982. The county is 52% Hispanic. African-Americans make up 7.2% of the population and Filipinos make up 2.4% of the population. 28% of the population is less than 18 years old. 12.5% of the males in the county are institutionalized. Since 2006 approximately 60% of all coccidioidomycosis cases in Kings County have been reported in state prisoners.

Incidence of CM in Kings County

Coccidioidomycosis is a reportable disease in California. Beginning in 2007 the Kings Co. Department of Public Health has tracked cases by clinical presentation at the time of the report. In the 4.8 year interval since 2006 ten cases of CM have been reported through the mandated disease reporting system. In this interval another nine cases have been identified. Six of these were identified through a review of all coccidioidomycosis related discharges from three Adventist Health hospitals in the region. Four of these cases were reported as coccidioidomycosis but not as CM. In two of the cases no report of any coccidioidal disease was made. The annual rate of CM in Kings County for this 4.8 year period is 3.4 cases/100,000. The incidence of all coccidioidal disease varies over time for unknown reasons. This observed rate may not be representative of longer intervals. On the other hand, CM may be significantly underreported in Kings County. Coccidioidal meningitis is not rare in Kings County.
The Disease and Outcome

“Meningitis is the most feared form of dissemination and is found in nearly one-half of individuals with disseminated disease. Before the advent of therapy, death within a few months was nearly universal.” [3]

While there were occasional case reports of multiyear survival from the pre-treatment era, the outcome of untreated CM was essentially always fatal. In one study of servicemen with CM as the only site of dissemination before any treatment of CM was available, all ten of the cases died within 31 months after the onset of CNS symptoms. The mean survival was 13 months. [4]

No treatment is known to cure CM and the diagnosis entails a lifetime of treatment. Prior to the advent of azole therapy, amphotericin was the sole agent available. Intravenous administration wasn’t effective. This drug had to be introduced into the cerebrospinal fluid. Intracisternal administration was less problematic that the intrathecal route. Despite this aggressive form of therapy, during the first two decades of the amphotericin treatment era 49 % (130/265) of the treated cases were known to have died of CM. [5] In the combined azole and amphotericin era Johnson and Einstein have estimated the current CM mortality rate at 30%. [3]

CM is known to cause extensive neuropathology. In an autopsy series of the brain from the pre-treatment era, n=15, in addition to basilar meningitis, ventriculitis, cerebritis, endarteritis obliterans, hydrocephalus and various cerebral white matter lesions were commonly noted. These findings were similar to the findings in another group, n=17, who received some form of amphotericin therapy. 88% of all the patients (28/32) had brain parenchymal lesions. In many cases the parenchymal lesions could be associated with ante-mortem neurologic deficits. In this population atherosclerotic changes were uncommon while endarteritis obliterans was frequently noted. The infarcts appeared likely due to CM associated endarteritis obliterans. [6]

On occasion CM vasculitis induced cerebral vascular accident may dominate the clinical course. Despite young age the patients who survive may have significant residual neurologic deficits such as aphasia and hemiparesis. [7]

Neuroimaging has also demonstrated neuropathology besides basilar meningitis. In one series 51.6% had hydrocephalus and 38.7% had cerebral infarct. Multiple findings were frequent. 11% of the cases had both hydrocephalus and infarct. The presence of either of these findings was associated with twelve fold increase in mortality over those patients with CM who had normal neuroimaging. [8] The six year mortality rate in this series, n=42, was 26%.

Communicating hydrocephalus is the most common complication of CM and signs and symptoms of hydrocephalus may be the presentation of illness that leads to the diagnosis of CM. The shunts used to treat hydrocephalus are subject to complications including migration, secondary bacterial infection, dissemination of the coccidioidal infection and malfunction. [9]

Active inflammation due to CM appears to be responsible for the development of the most common complications of CM, hydrocephalus and cerebral infarction. [3,9] Dr. Blair has opined that the onset of hydrocephalus is “related to the duration of the meningitis before diagnosis and initiation of treatment”. While both of these conditions may occur in treated patients, early and continuous treatment may decrease the frequency or delay the onset of these serious complications. Treatment clearly decreases mortality. Early initiation of treatment would appear highly preferable to delayed treatment.
Diagnosis

Most but not all cases have a prior diagnosis or a history compatible with primary pulmonary coccidioidomycosis. In one series, of 21 patients with a preceding pulmonary illness the interval between onset of pulmonary disease and meningitis was less than a month in 7 cases (33%); one to six months in 9 cases (43%); 1.5-12.5 years in 5 cases (24%). Evidence of other coccidioidal disease is common at the time of CM diagnosis. In another series, 68% (24/35) of the patients had evidence of pulmonary disease at the time of the diagnosis of CM. Twenty per cent (7/35) had evidence of extrameningeal dissemination.

In most cases the diagnosis and management of coccidioidomycosis is dependent on the assessment of coccidioidal antibodies in the blood with rising complement fixation titers leading to concerns about metapulmonary dissemination. The observed blood CF titers in cases of CM can be minimally elevated, e.g., 1:2 or 1:4. The CF titer in the blood can not be used to exclude the diagnosis of CM.

Neuroimaging is useful in the evaluation of CM but can not be used to reliably exclude the condition. MRI is more sensitive than CT but may be falsely negative early in the disease process. In one study 29% (4/14) of patients had a negative MRI examination early in their course. In another study CT examination was abnormal in only 42% (20/48) of patients with CM.

The symptoms and signs of CM are varied, nonspecific and not consistently present. Many authors list such findings as altered mental status, personality changes, gait abnormalities, focal neurologic defects and even nausea and vomiting as signs suggestive of CM. These findings may more properly be seen as more consistent with the complications of CM such as hydrocephalus or cerebral infarct. Presumably they would be more likely to be found in patients with abnormal neuroimaging examinations. Fifty years ago Dr. William Winn suggested a more restricted range of signs and symptoms: “Persistent headache or neckache, accompanied by increasing lassitude and drowsiness and low grade fever, may herald meningeal involvement.”

Headache is the most common complaint heralding CM onset noted in the literature. As headache may be associated with uncomplicated primary coccidioidal disease or treatment, headache per se is only somewhat helpful in the early recognition of CM.

Doctors Johnson and Einstein have opined that approximately 50% of patients will exhibit “some degree of meningismus.” The VA-Armed Forces study noted nuchal rigidity in 33% (8/24) of their cases. Dr. Winn, no doubt, recognized that the clinical signs and symptoms for CM were soft fifty years ago. “Coccidioidal meningitis, notorious for its insidious onset, requires a high degree of alert anticipation.” It would appear that this hasn’t changed in the intervening years.

Lumbar puncture and examination of the cerebrospinal fluid remain the definitive means of diagnosing CM. The opening pressure may be elevated or normal. Pleocytosis will be present. Typically the cell counts will be few to several hundred. Early in the course polymorphonuclear cells predominate similar to asceptic meningitis while later lymphocytes and mononuclear cells will predominate. The protein will usually be elevated and the glucose will usually be modestly depressed. Coccidioidomycosis is the one fungal infection associated with CSF eosinophilia. In an endemic area such as
Kings County, C. immitis is probably the most common etiology of eosinophilic meningitis. In a retrospective chart review in patients with CM 1986-1991 in Kern County 70% of patients had eosinophilic meningitis. [12] This finding in an appropriate clinical setting should raise concern for coccidioidal infection. Positive culture or pathology examination are diagnostic when positive but neither is frequently present. The diagnosis of CM is confirmed by the finding of complement-fixing antibodies in the CSF. (Enzyme immunoassay and latex agglutination tests should not be relied on for CSF testing.) Initial CSF serology may be negative but will become positive with later testing. A negative CSF serology doesn’t rule out the diagnosis of CM. [9]

**Treatment**

As noted previously, intrathecal or intracisternal amphotericin was for many years the only treatment available for CM. Over the last two decades azole therapy has become the most common treatment for CM with general agreement among treatment experts that azole treatment should be continued indefinitely [3,9,13,14,15]. In one study fourteen of eighteen patients relapsed after discontinuing prolonged azole treatment courses. The interval between relapse and discontinued therapy ranged from 0.5 to 30 months. Three of the relapses were fatal [16].

Because pregnancy may reactivate CM, some experts discourage pregnancy in women with CM [3]. Azole antifungals may be teratogenic, especially early in pregnancy. Women wishing to become pregnant may elect to be treated with intrathecal amphotericin during their first trimester [17]. Long term azole therapy in fertile women needs to be linked to effective contraception and to planned pregnancy should that be desired.

Patients co-infected with human immunodeficiency virus will have a poor prognosis if the HIV infection isn’t adequately treated. In the pre-HRT era, the six month fatality rate of CM patients co-infected with HIV was 33% [18]. All patients with CM, or any form coccidioidomycosis, should be screened for HIV co-infection.

**Public Health Considerations**

Arguably a case has been made for a low threshold for performing lumbar punctures. The clinical indications for an LP in the evaluation of a patient for coccidioidal meningitis likely are less dramatic than those in other clinical conditions necessitating the procedure. With the threshold set appropriately, many of the resulting cerebrospinal fluid examinations should be normal. With early diagnosis of CM chosen as a goal in coccidioidal endemic communities the frequency of LP procedures should increase. Is this service easily accessed in Kings County?

This procedure may not be readily available. Based on an informal survey the procedure is now infrequently available in the primary care setting. One respondent stated: “It was easy to do a lumbar puncture in the 60’s and 70’s – even in the office. Now it requires a neurologist, a neurosurgeon and a CT scan first! Everyone is afraid these days.” Another respondent noted that likely a primary care physician would have to refer the patient to the emergency department where the procedure may not be deemed clinically indicated by the emergency department physician. Timely evaluation by a neurologist or neurosurgeon often would be neither necessary nor available.
Adventist Health Central Valley Network has expressed an interest in developing this service as a community benefit. This paper was partially written to further discussions about developing the service. Adventist Health is a significant health care provider in Kings, Fresno and Tulare Counties, all coccidioidomycosis endemic counties.

The early diagnosis of CM is pointless unless continuous treatment is also assured. Medication cost and prior authorization may hinder the goal of continuous treatment. The Kings County Department of Public Health in partnership with the California Department of Public health has been successful in removing fluconazole prior authorization under the MediCal program. We’ve also had success in providing fluconazole at very reduced cost through the 340 B Prime Vendor Program. The department is available to work with community providers to assure that treatment is available. The department would like to partner with clinical and pharmacy providers in the county to develop guidelines for facilitating and assuring treatment adherence.

There may be a need for provider education. The department hopes to partner with the provider community to identify the educational needs and to assist in development of the training.

Education of the general community may be more problematic. The condition isn’t common and the community has many other concerns. The department will develop materials for its webpage. The department can, if desired, develop and make available to community providers patient education materials. Other recommendations regarding community education are welcomed.

To improve CM surveillance in Kings County the department is considering mandating that all cases of CM be reportable, even when another form of coccidioidomycosis has previously been reported. Input from the provider community regarding this proposed new mandate is welcomed.

The department will invite health departments in other endemic counties to partner in the development of provider and patient education materials. Other endemic counties may also decide to improve CM surveillance by mandating CM reporting.

Although Coccidioidal meningitis is not a common disease in Kings County, it is a very significant condition for the affected population. A community based approach to addressing CM in Kings County can be expected to result in better outcomes.

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References