Coccidioidomycosis of the Meninges

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SUMMARY

In a review of 53 cases of coccidioidal disease, 50 of which resulted in death, some symptoms were noted to be so common as to facilitate diagnosis. Laboratory studies of spinal fluid gave helpful information. Particularly noteworthy with regard to roentgenologic studies was the fact that in no case in which there was pulmonary cavity formation due to coccidioidomycosis did coccidioidal meningitis develop.

IN the last approximately 50 years coccidioidomycosis due to coccidioides immitis has been an important public health and medical problem in Central California, particularly in the southern end of the San Joaquin Valley.

In any discussion of coccidioidal granuloma, coccidioidomycosis of the meninges is an important phase.

Smith[2] and co-workers in a review of the literature stated that this mycotic infection has been noted to be endemic in western Texas along the Mexican border, in southern New Mexico, in southern and central Arizona, in southwest Utah and in the southern tip of Nevada. In California the disease is endemic in the southern San Joaquin Valley with irregular distribution up as far north as Modesto, Merced and Tracy, and in eastern Ventura and Santa Barbara counties. In southern California some cases have been reported in San Bernardino, Riverside and San Diego counties.

Because there is so much traveling by the general public, physicians will be on the alert for this disease not only in western United States, but also in other areas of the country.

Now that coccidioidal granuloma has been added to the list of reportable diseases, it is to be expected that a continual study of this disease will have additional significance to health officers in California.

All of the areas in which coccidioidomycosis is endemic are arid or semi-arid. The common finding is that the onset of the majority of the cases of coccidioidal meningitis within the boundaries of Kern County has been in the period May through November. However, the severity and frequency of dust storms occurring even in the so-called wet season implies that coccidioidal granuloma, with or without meningitis as a complication, may occur at any time during the year.

Physicians working in the Kern County Hospital and Health Department have estimated unofficially that some 67 cases diagnosed as coccidioidomycosis of the meninges have occurred in Kern County in the 13 years since 1936. Since reporting has not been complete and errors have occurred in the differential diagnosis of coccidioidomycosis of the meninges in this group of cases, this presentation will consider 53 selected cases. The diagnosis in each instance was confirmed by clinical, laboratory, biopsy and, in many instances, autopsy evidence.

Of the first 147 known and reported cases of coccidioidal granuloma that occurred in Kern County from 1901 to 1936, 67 were fatal. Of the 67 patients who died, only nine were stated to have had coccidioidal meningitis. It is interesting to note that three of the first four Kern County patients reported to have died of the disease were reported to have had coccidioidal meningitis.*

In a study by Kirshbaum† of 53 fatal cases of coccidioidal granuloma in Kern County, it was noted that 29 of the 53 patients also had coccidioidomycosis of the meninges. Kirshbaum felt that the lymphatic system acts as a barrier preventing dissemination to the meninges; upon a hematogenesis basis, fatal meningitis might have developed in even a greater proportion of cases.

Generally the incidence of coccidioidomycosis of the meninges is about twice as great in males as it is in females. In the age group 20 to 40 years there is even greater disparity; in this age span almost thrice as many men as women are affected. There is also a relatively higher incidence in Indians, Filipinos, Negroes, and Chinese than in white persons. Although the non-white group constitutes only about 8 per cent of the population in Kern County, almost 50 per cent of the total cases of coccidioidal meningitis have occurred among them.

Gifford,[1] in a study of coccidioidomycosis in Kern County which she reported in 1939, noted not only this disparity in incidence with regard to race and sex, but also that the death rate was considerably greater among males than females. She also called attention to the fact that in recent years more

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* From a study made by M. A. Gifford, M.D., for the Kern County Health Department.

† J. Kirshbaum, M.D., who then was pathologist at Kern General Hospital.

of the non-granulomatous, non-fatal type of coccidioidal disease had been reported and that more of these cases were reported in women than in men.

In the present study of 53 cases of coccidioidal meningitis few changes were noted with regard to factors of incidence relative to age, race, sex, occupation and area of habitation. Once more endemic foci have been shown in rural areas about Bakersfield, Delano, Shafter, Arvin, Wasco, and the Greenfield and Lakebottom areas. Fifty per cent of these cases of coccidioidomycosis of the meninges occurred in persons employed in the agricultural industry. More than 80 per cent of the patients who died were engaged in work in which dust could well have been an occupational hazard.

In the series here under consideration, the diagnosis was established by various means—by history, physical findings, laboratory studies, biopsy, and autopsy. A high index of clinical suspicion was developed as a result of the frequently common findings in the typical cases of coccidioidal meningitis.

Headache, often severe, persistent and resistant to routine treatment, was one of the common symptoms in the older patients; there were only a few who did not have frontal and occipital headache. (In many cases this symptom was relieved by timely aspiration of spinal fluid.)

Signs of meningeal irritation were common. Severe stiffness of the neck and spasms of the neck muscles were noted in most cases. Symptoms related to the eyes consisted of photophobia, blurring of vision and diplopia. Chest and abdominal pain was less common, although when pleurisy or pneumonitis (as confirmed by x-ray) persisted, the chest pain was more severe.

Subjective mental aberrations frequently were noted in association with headache, neck stiffness, and chest pain. Loss of memory, disorientation, comatose stages, paraphasia and other mental changes were observed, particularly in the terminal stages of meningitis.

Usually there was steady fever of several degrees. In a few cases there was no febrile stage. In terminal phases and with onset of complications the fever was explosive and very high. In some cases 106° to 107° F. was observed before death.

In many of the cases the early symptoms were insidious and presented difficulty in the problem of differential diagnosis. Among the diseases that most often had to be considered in differentiation were tuberculous and influenzal meningitis, purulent bacterial disease of the meninges, poliomyelitis, arthropod-borne encephalitis, post-viral encephalitis (measles, mumps, etc.), and prodromal stages of typhoid fever, dysentery diseases and pneumonia.

In a previous study carried out by Smith, Gifford and others, it was found that positive reaction to a skin test occurred usually in nine to 11 days after onset of illness with coccidioidomycosis. However, in cases of coccidioidomycosis of the meninges, since the disease was a part of a chronic disseminated pattern, it was noted that many of the patients were anergic. In only three such cases was there positive reaction, and in all three it occurred during the terminal month of illness. Although in most of the cases both mantoux and coccidioidin skin tests were done as early as possible after coccidioidomycosis was suspected, by and large the skin tests were of little value in making the final diagnosis. In two cases of coccidioidal meningitis, tuberculous and coccidioidal infection were concurrent; one of the patients had tuberculous meningitis as well as coccidioidal meningitis.

Two other very common observations in these cases were:

1. In many instances absence of evidence of lesions in x-ray films of the chest was important in helping to exclude tuberculosis. In only a few cases was there active mycotic pulmonary disease, as determined by x-ray or necropsy, at the time of death.

2. Although the primary portal of entry was pulmonary, there were no instances of cough that was more than transitory and non-productive in nature.

Results of laboratory studies were valuable aids in diagnosis. Examination of the spinal fluid was most helpful. In only one instance was the spinal fluid cell count normal; and in only one instance was the count more than 3,000 cells for each cubic mm. In about 90 per cent of the cases, cells in the spinal fluid numbered between 200 and 1,300. The spinal fluid was drawn soon after the onset of meningeal involvement. In the few instances in which the spinal fluid pressure was measured, it was above normal; commonly, 270 to 300 mm. of water was noted as the initial pressure. The pressure was reduced upon the removal of 15 to 30 cc. of fluid. In the average case the fluid was slightly cloudy to clear; in some instances it was xanthochromic or light green and of gelatinous consistency. In two cases in which clear spinal fluid was incubated for 24 to 48 hours a fungoid growth (later identified as coccidioides immitis) was obtained. In some cases a very heavy pellicle formed in the specimen of fluid within 24 hours, but in only one such instance was coccidioides immitis isolated. In seven cases the diagnosis was established by growth on cultures of gastric washings. Examination of direct smears and results of cultures on Sabaroud's media and other media frequently disclosed no coccidioides.

In tests on the spinal fluid, the colloidal gold curve was significant. In about 90 per cent of the cases there were colorimetric changes to the left of the color zone similar to that seen in paresis.

In only a few cases did coccidioidomycosis develop in guinea pigs that were inoculated with spinal fluid from the patients. Total protein content of the spinal fluid was abnormally high in more than 75 per cent of cases. In the spinal fluid of some patients the total protein was 150 mg. or more per 100 cc. The differential cell count of fluid taken in the early stages of illness showed up to 100 per cent polymorphonuclear cells in some instances. Frequently there was a preponderance of polymorpho-

nuclear cells in early specimens, with a gradual decrease later and a corresponding increase in lymphocytes. Almost complete spinal fluid block was observed clinically in two cases, and in one of the two, postmortem examinations proved this clinical assumption to have been correct. The number of cells in the spinal fluid did not have any direct relation to the severity of the illness.

Results of urinalysis were not of definite diagnostic help. Blood cell counts, which were done routinely in many instances, showed little diagnostic value. Leukocytes frequently numbered between 10,000 and 14,000, with polymorphonuclear cells relatively increased in number. In a few cases eosinophilia was noted in differential count of leukocytes. Secondary anemia was noted in a few instances.

The sedimentation rate of blood taken from the more acutely ill patients was accelerated, and this information was of some value in determining prognosis. The greatest value gleaned from determination of sedimentation rate, however, lay in the help it gave toward completion of diagnosis and, in some cases, in excluding other than the correct diagnosis.

Serology tests done on serial specimens of blood and spinal fluid sent to Stanford University School of Medicine were helpful. In serial dilution, precipitin and complement fixation antibodies were observed in many cases. Complement fixation antibodies were last to appear, and the persistence of antibodies, especially in high dilution, sounded a serious prognostic note. With few exceptions, heavy antibody formation was associated with clinical severity of the illness.

X-ray findings of disease in the chest and other areas, particularly bone, were helpful in those cases in which the disease was widely disseminated. Furthermore, roentgenologic evidence of pulmonary cavities due to coccidioidomycosis was profoundly important, for in no case of meningitis due to coccidioides was there pulmonary cavity formation. When pulmonary cavity formation existed in coccidioidal infection, the course of illness was benign.

In the fatal cases of coccidioidal meningitis in the present series, the duration of the illness varied from six weeks to about two years. Of the 53 patients, 15 died within three months after onset of acute illness, 23 within 12 months; seven lived more than one year and two lived almost two years. In three cases the duration of illness was not known, and three patients known to have coccidioidal meningitis are still living.

AUTOPSY

In 35 of the 53 cases the presence of coccidioidomycosis of the meninges was confirmed by postmortem findings. In each instance most of the pathologic changes noted were at the base of the brain and in the meninges. It was noted generally that the meninges were thickened and edematous and the vessels hyperemic. In many of the cases there was a definite exudate over much of the total brain area. The exudate, in a number of cases, surrounded the nerve roots. In those cases in which the disease had been of the more chronic nature, very frequently the convolutions of the brain were thickened and the meninges were thin. On examination of sections it was noted that the ventricles in most instances were dilated and filled with clear or straw-colored spinal fluid.

Epithelioid cells were frequently noted in microscopic studies of exudate from the base of the brain, the pons and the medulla. Heavy infiltrations of plasma cells, round cells and eosinophilic leukocytes were a common observation. There were frequently scattered giant cells. In some instances the coccidioides spherules were conspicuous, in others not. Areas of necrosis and numerous elements of fibrocellular proliferation were observed in some of the sectioned material.

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REFERENCES

1. Gifford, M. A.: Coccidioidomycosis, Kern County, for the Session on Fungus Infections, Sixth Pacific Science Congress of the Pacific Science Association, August 2, 1939.

2. Smith, C. E.: Coccidioides immitis, Farlowia, 2:199, July 1943.

3. Smith, C. E.: Recent progress in pulmonary mycotic infections, California Medicine, 67:179, September 1947.

4. Smith, C. E., Beard, R. R., Rosenberger, H. G., and Whiting, E. G.: Effect of season and dust control on coccidioidomycosis, J.A.M.A., 132:833, Dec. 7, 1946.

5. Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G.: Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases, Am. J. Pub. Health, 36:1394, December 1946.