Outbreak of Histoplasmosis in a School Party That Visited a Cave in Belize: Role of Antigen Testing in Diagnosis

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Histoplasmosis is endemic in parts of South and Central America and the role of bat guano is widely recognized in promoting the growth of the organism.1,2 Previous outbreaks have been reported among cavers in the United States3,4 and South America,5 often in travelers upon return to their home country. The illness may be quite severe, as the exposure is often extensive, emphasizing the importance of recognition of the risk for histoplasmosis in cavers and understanding the approach to diagnosis.

Thirteen students (aged 16 to 18 years) and 2 teachers from a school in Trail, British Columbia, Canada, traveled in Belize with 2 guides (1 Canadian, 1 from Belize) from March 16 to 26, 2000. Local BC physicians reported complaints of fever and chills in returning travelers to the BC Centre for Disease Control (BCCDC).

Method

Two physicians from BCCDC flew to Trail on April 12, 2000 to investigate the outbreak. Information collected by local public health staff, available chest x-rays, and laboratory results were reviewed. Trip and symptom details were obtained from one of the teachers. A standard questionnaire, aimed to identify potential risk factors and symptoms, was developed. The questionnaire was administered, and blood and urine samples were obtained, at the high school on April 13. An enzyme-linked immunoassay (EIA) was used to detect histoplasma antigen in serum and urine; and has been previously described.6 Results, expressed as enzyme immunoassay units, of 1 unit or higher are regarded as positive.

On May 25, a second questionnaire to determine symptom duration was administered at the school and convalescent serology and urine samples obtained. Telephone follow up of those reporting persisting symptoms was attempted.

Results

Sixteen initial questionnaires were completed; all 13 students (one by telephone); both teachers and the Canadian guide who faxed his response. No contact was possible with the guide from Belize. The prime focus of the trip involved salt water kayaking between islands and camping on the beaches. On March 18, all students, staff, and both guides had a 3-hour excursion into a cave where bats were present. At times, headroom was limited so the party crawled on the dry cave floor in bat guano.

Illness Profile

Fourteen individuals reported being ill following their return to Canada (attack rate of 87.5%); one student and the Canadian guide remained well. The symptom onset dates were April 2–9 (days 15–22 post bat cave exposure); Figure 1. All who were unwell complained of headaches, chills, sweats, and muscle aches (mainly of the
back and neck), which were generally worse later in the day. Twelve persons reported a fever; most felt unusually tired and light-headed, and 9 reported joint symptoms. Although not noted as a major complaint at the initial public health nurse interviews, reported respiratory symptoms were common: 11 had shortness of breath; 10 had chest pains; 8 a sore throat; and 8 had a cough. Other symptoms reported were nausea (5 persons); abdominal pain (6); swollen lymph nodes (2); no rashes or other skin complaints were reported or seen. By April 13, 9 individuals had seen a physician since their return to Canada; 7 reported improvement in their symptoms; 3 reported no improvement; and 4 reported symptoms were worse.

Fifteen follow-up questionnaires, 14 convalescent urine, and 10 convalescent serum specimens were obtained. Of the 14 questionnaire respondents who had been ill, 10 reported feeling completely better, and 4 were improving. Follow up of these 4 was attempted; 1 reported symptoms lasting 60 days but contact with the other 3 has not been possible. Ten (71%) of those who fell ill, experienced symptoms attributed to histoplasmosis lasting 18–27 days; 4 (29%) were ill for more than 50 days.

**Laboratory Results**

Thick and thin smears for malaria, spirochetes and trypanosomes, dengue serology, histoplasma antibody and antigen tests on all 10 serum samples obtained on day 26 post bat cave exposure were negative. Seven urine samples, also obtained within a month of exposure, were tested for histoplasma antigen: 5 were positive; 2 were negative (1 of these was from the asymptomatic student). Urinary antigen was not detected in follow-up urine specimens from 14 travelers. Convalescent serum specimens (> 2 months postexposure) were available for 10 travelers: 2 were positive for M antibody to histoplasma (both students had not provided urine samples in April); 1 additional individual (who was positive for urine antigen in April) had both M and H antibody to histoplasma. Thus, overall 7 of the 15 student/teacher-group tested positive for histoplasma antigen (4), antibody (2), or both (1). No specimens were available from the Canadian guide.

**Chest X-ray Results**

Four cases had chest x-rays performed: 1 was reported as normal; 1 showed a well-defined nodule of the left upper lobe; the third had patchy basal infiltrate but no pulmonary nodularity; a fourth demonstrated a faint nodule in the right upper lobe, which had resolved on a follow-up chest x-ray. The acute and convalescent urine antigen tests of the student with a well-defined nodule were negative (unfortunately no convalescent serum was available for antibody testing); however, this student reported debilitating symptoms continuing for 3 months after exposure so was given an oral antifungal regimen (itraconazole 200 mg bid for 6 weeks) with marked improvement in symptoms.

**Discussion**

*Histoplasma capsulatum*, a spore producing dimorphic fungus, is endemic through much of the world including the United States and Central and South America. The role of bird and bat guano is widely recognized in promoting the growth of the organism in soil by providing a source of nitrates, which accelerate spore formation. Bats, unlike birds, may themselves become infected with *H. capsulatum*. The severity of illness after inhalation exposure to *H. capsulatum* depends on the intensity of exposure and the immunity of the host. Most patients who acquire histoplasmosis remain asymptomatic, the only sign of a past exposure being a positive intradermal histoplasmin test. Inapparent infections are very common in endemic areas and usually result in increased resistance to infection. Heavy exposure can cause severe diffuse pulmonary infection. Treatment is not usually indicated because the illness is self limited and associated with minimal morbidity. Therapy may be helpful in symptomatic patients whose conditions have not improved during the first month of infection. Fever persisting for >3 weeks may indicate development of progressive disseminated disease, which may be aborted by therapy. Only one of the students who visited Belize required an oral antifungal regimen with marked improvement of their symptoms.

This study shows the potential role of antigen testing for diagnosis of acute histoplasmosis. Antigen was detected in the urine of 5 of 7 subjects tested within the first month of exposure, for a sensitivity of 71% in acute histoplasmosis. Similar findings were observed in a study by one of the authors (LJW) during an outbreak in a
prison; antigenuria was detected in 20 of 24 (83%) prisoners. None of those who caved in Belize exhibited antigenemia, showing the greater sensitivity of urine testing in acute histoplasmosis. Other studies have shown the serologic response to be poor in the first month after exposure. The sensitivity of antigen detection is lower in patients with subacute pulmonary histoplasmosis (about 30%) or chronic pulmonary histoplasmosis (15%). Thus urine antigen testing is most useful for patients with acute presentations following exposure to a site suspected to be contaminated with H. capsulatum or with diffuse pulmonary infiltrates. Urine testing also should be performed in persons presenting within a month of presumed exposure to identify cases before the development of antibodies. Antigen testing may permit a rapid (1 day turn-around-time) diagnosis in such cases.

In other studies, 75–80% of subjects exhibited an antibody response, supporting the need for convalescent antibody testing. However, antibodies were detected in only 3 of 10 (30%) convalescent sera from the Belize cavers. Possible explanations for this discrepancy include differences in sensitivity of the testing methods (complement fixation tests are more sensitive than the immunodiffusion technique used in this study), timing of specimens, or intensity of exposure.

H. capsulatum has not been known to cause illness in BC, but it is not a reportable disease. All 25 histoplasmin skin tests performed as part of an illness survey of students with respiratory symptoms in northern BC were negative. Fewer years of caving experience, longer time spent in the caves, and entering a confined crawl space have been found to be risk factors for histoplasmosis illness. The high attack rate of histoplasmosis of the Belize travelers (87.5%) is remarkably consistent with that found in a group of university students who entered a cave inhabited by bats in Costa Rica (88%). H. capsulatum has been more readily isolated from caves under dry conditions. The high attack rate of the Belize travelers may possibly be attributed to a number of factors: the young age of the travelers, lack of previous exposure, and the large inoculum of spores to which they were exposed crawling in the dry bat guano on the cave floor.

In summary, this report emphasizes the risk for histoplasmosis among cavers. The risk of acquiring histoplasmosis must be considered by any tour operator or traveler contemplating cave exploration in Central or South America; outbreaks have occurred among individuals exploring caves in the United States, including caves outside the endemic area. Health care providers should include histoplasmosis in their differential diagnoses of travelers to endemic areas complaining of fever and chills and ask about cave exposure. We have also demonstrated the potential usefulness of urine antigen testing and the limitations of serologic testing for diagnosis of acute histoplasmosis.

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References