Rat-Bite Fever \textit{(Streptobacillus moniliformis):} A Potential Emerging Disease

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\textbf{ABSTRACT}

\textbf{Objectives:} To determine the relative prevalence of human infections attributable to \textit{Streptobacillus moniliformis} in California over the past 3 decades.

\textbf{Methods:} A retrospective analysis of all the data collected was conducted on \textit{S. moniliformis} cultures identified by the Microbial Diseases Laboratory (MDL) from January 1970 to December 1998.

\textbf{Results:} Information on a total of 45 \textit{S. moniliformis} isolates was analyzed. Overall, 91\% of the isolates were from human sources; 58\% were received since 1990. These strains were divided almost equally between males and females, with 50\% of the isolates from patients 9 years old or younger. In 75\% of the cases of human infections where a diagnosis was given, rat-bite fever (RBF) was suspected; 83\% of these suspected cases involved either a known rat bite or exposure to rodents.

\textbf{Conclusions:} As crowding becomes an increasing environmental reality, humans are more frequently being exposed to zoonotic diseases as a result of encounters with "wild" animals. Domesticated animals also are exposed more frequently to wild animals; thus, increasing human exposure to once rare zoonotic illnesses. Rat-bite fever is a disease that seems to be easily recognizable by clinicians, easily identified in the clinical laboratory (if suspected), and successfully treated when the appropriate therapy is administered. Physicians should consider RBF as a possible diagnosis when fever, rash, and exposure to rats are part of the patient's history.

Key Words: rat-bite fever, \textit{Streptobacillus moniliformis}, zoonotic infections


A seldom encountered zoonotic pathogen seen by clinical laboratories is \textit{Streptobacillus moniliformis}. This pleomorphic, facultatively anaerobic, gram-negative bacterium is traditionally associated with direct or indirect exposure to rats, the natural reservoir for \textit{S. moniliformis}. Its distribution is worldwide.\textsuperscript{1-3}

Two distinct clinical syndromes have been identified in association with \textit{S. moniliformis} infection. One, Haverhill fever, originally recognized in 1926, is an infection transmitted to humans through the consumption of contaminated water, milk, or food previously in contact with rats.\textsuperscript{4,5} The disease is characterized by a high incidence of pharyngitis and pronounced vomiting.

The more common syndrome associated with \textit{S. moniliformis} infection, however, is rat-bite fever (RBF). This illness is characterized by abrupt onset of high fevers, headaches, severe migratory arthralgia, vomiting, and a rash (2–4 days later). The petechial rash develops over the extremities, in particular the palms and the soles.\textsuperscript{2} The onset of symptoms typically occurs 10 or more days after exposure. Any related wound has usually healed by the time symptoms develop.\textsuperscript{1-4} Estimates of the mortality rate associated with untreated cases of streptobacilliosis approach 13\%,\textsuperscript{5,6} Fatality is most often associated with cases in infants and patients with endocarditis.\textsuperscript{1,5}

To date, most of the information regarding \textit{S. moniliformis} infection, and in particular RBF stems from individual case reports. In light of the increasing incidence of human contact with animals, including the care and handling of unusual or exotic pets,\textsuperscript{7} a retrospective review of the incidence of streptobacilliosis in California over the past 3 decades was conducted and serves as the basis of this report.

\textbf{MATERIALS AND METHODS}

The Microbial Diseases Laboratory (MDL) is the reference laboratory for the state of California. The laboratory is responsible for the isolation and identification of bacterial, fungal, and parasitic pathogens of public health significance throughout the state. A system of 39 county public health laboratories serves as the conduit for the submission of unusual, unidentified, or reportable isolates from clinical laboratories to the MDL.

The MDL identifies or confirms \textit{S. moniliformis} isolates using four tests: (1) a growth requirement of 10 to 20\% serum; (2) the presence of typical gram-negative bacilli (sometimes in chains) and filaments with bulbous swellings in a Gram stain (Figure 1); (3) growth in broth (thioglycollate medium) with "puff ball"-colony formation (Figure 2); and (4) a positive direct fluorescent antibody test using...
an in-house produced polyclonal antibody. The polyclonal antibody was prepared from whole cell antigens of *S. moniliformis* strain MDL 56-3. Formalized whole cell antigen was washed and used to immunize rabbits. Rabbits were immunized five times over a 2-week period by intravenous injection through the marginal vein. Serum was collected and fluorescein isothiocyanate (FITC) conjugated. Quality control was performed on the conjugate by testing it against various *S. moniliformis* strains at several working dilutions. Original laboratory reports were reviewed and data from these were compiled to produce the results.

**RESULTS**

Since 1970, the MDL has received 45 isolates of *S. moniliformis*. Forty-one (91%) isolates were from human sources; of these, 24 (58%) have been received since 1990 (Figure 3). These 41 isolates were received from 19 different local (county) jurisdictions, with a majority of strains (61%) received from four county and one city public health laboratories: Sacramento (n = 8), Los Angeles (n = 6), Santa Clara (n = 5), San Diego and San Francisco (n = 3 each). Most infections were centered around densely populated areas and no infections were reported from northern California counties. Geographically, the 41 *S. moniliformis* infections were from southern California (n = 14), the San Francisco Bay area (n = 11), the San Joaquin valley (n = 9), North San Francisco Bay area (n = 3), Monterey Bay area (n = 3), and Sierra Foothills (n = 1). The male to female ratio was 1:0.1:2 with 19 (46%) male and 22 (54%) female patients. The age ranged from 6 weeks to 92 years (mean, 46 y) (Figure 4). The average age was just under 19 years.

The most common isolate source of *S. moniliformis* in human infections was blood (78%), followed by aspirates (12%) and wounds (10%). Common media used to isolate *S. moniliformis* from blood included pediatric BACTEC™ Plus blood culture bottles (BD Diagnostics, Sparks, MD) (n = 5), trypticase soy blood culture bottles, with or without supplementation (n = 4), anaerobic blood culture bottles (type not specified, n = 3), and thioglycollate broth (n = 1). For nonblood isolates (e.g., wounds) blood agar was the most common media used to recover *S. moniliformis*. Some of the histories included the number of times *S. moniliformis* was isolated from the blood per patient (n = 28); the results were as follows: 17 (61%) were isolated once, eight (29%) were isolated twice, and three (10%) were isolated three or more times. From the other sources with this information (n = 5), four (80%) were isolated only once per patient, and the remaining wound isolate was positive by culture more than three times. The range of onset times (n = 9) was 2 to 7 days, with four (44%) patients exhibiting symptoms within 3...
days of exposure. Table 1 lists selected characteristics of the patients in this study.

When patients presented with at least two of the three classic symptoms (fever, rash, arthritis) and a history of rat exposure, clinicians suspected RBF in 44% of the cases. Another 19% were diagnosed with RBF if there was an exposure to rats but only one of the three classic symptoms. One astute practitioner diagnosed RBF in a patient with no history of exposure to rats or any of the three major symptoms. In patients presenting with at least two of the major symptoms and having a history of a different animal exposure (to a mouse and a squirrel, respectively), two clinicians suspected RBF. Several authors have reported RBF following exposures to animals other than rats.1,5

Symptom combinations varied greatly in the cases included in this study. The greatest percentage of the patients exhibited fever with rash (28%), followed by patients having all three classic symptoms: fever, rash, and arthritis (22%). Several histories showed fever with arthritis (17%). Only one patient had a rash with arthritis and no fever. Four of the cases (11%) had fever without rash or arthritis.

In the present study, exposure to pet rats accounted for the greatest risk. All the pet rat exposures except one took place in the owner's or a friend's home. The exception occurred in a pet store. This source of exposure is not commonly acknowledged in the current literature as the greatest risk. Three of the school rat exposures were to adults in school and could more accurately be classified laboratory exposures. All four other rat exposures were rat bites with the "source" of the rat not recorded in the exposure history.

Data confirm that transmission of S. montiiormis to humans by rats takes place not only after a bite.1-3,5 Thirty-nine percent of the cases received the pathogen as the result of exposure other than a bite that included scratches, kissing, or unknown mode of transmission.

In two of the patients treated with ampicillin-amoxicillin or ampicillin and clavulanic acid, gentamicin was also part of the regime. The "other antibiotics" category in Table 1 includes six patients treated with a variety of antibiotics, including erythromycin-tetracycline-clindamycin, cefotaxime, cephalosporins, cephalothin-cephalexin, doxycycline, and gentamicin.
DISCUSSION

The MDL has confirmed 41 cases of *S. moniliformis* associated with RBF between 1970 and 1998. Because this disease is not reportable, the incidence is difficult to measure. Overall numbers (1.5 cases/y), however, coincide with one report citing an incidence of one to two cases per year. Twenty-four isolates were received since 1990 (3.0 cases/y), suggesting a twofold increase and a possible rise in the incidence of RBF. Potential reasons for this increase include more pet and other animal exposure, better isolation and identification procedures, a higher level of suspicion on the part of clinicians, or some combination of these three.

Most RBF infections in California occur in younger people (under 12 y) and are associated with septic fever episodes. In addition, a large percentage of patients (67%) presented with signs of arthritis. Although *S. moniliformis* was more often isolated from blood than any other site, in four cases *S. moniliformis* was recovered from wounds or lesions. This is somewhat unusual in that classic descriptions suggest that wounds usually have healed by the time symptoms appear and the RBF diagnosis is entertained. Depending on whether or not a rash or polyarthritis accompanies febrile episodes of RBF, the differential diagnosis can also include brucellosis, leptospirosis, Rocky Mountain spotted fever, Lyme disease, viral exanthems, disseminated sexually-transmitted diseases, and a variety of other infective or vascular processes. Whenever a history of exposure to rats is revealed, RBF is highly suggested.

Several findings from this retrospective study are noteworthy. Two cases of RBF were associated with exposure to animals other than rats (squirrel, mice). This illustrates that the diagnosis of RBF cannot be ruled out solely on the basis of lack of exposure to rats. Another interesting finding is that in 29% of the cases, transmission of *S. moniliformis* via rat bites or scratches could not be documented. For one young girl, the apparent route of infection was more often isolated from blood than any other site, and in four cases *S. moniliformis* was recovered from wounds or lesions. This is somewhat unusual in that classic descriptions suggest that wounds usually have healed by the time symptoms appear and the RBF diagnosis is entertained. Depending on whether or not a rash or polyarthritis accompanies febrile episodes of RBF, the differential diagnosis can also include brucellosis, leptospirosis, Rocky Mountain spotted fever, Lyme disease, viral exanthems, disseminated sexually-transmitted diseases, and a variety of other infective or vascular processes. Whenever a history of exposure to rats is revealed, RBF is highly suggested.

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CONCLUSION

Increasing exposure to unusual, exotic, or wild animals leading to a rise in the frequency of zoonotic diseases is becoming a more common occurrence. This factor combined with the gradual urbanization of previously rural areas compounds the risk of exposure. The increasing contact between domestic animals, exotic pets, and wildlife increases the likelihood that transmission of zoonotic diseases among these groups of animals will occur, precipitating a rise in zoonotic disease in humans.

Although it cannot be unequivocally established that the increase in *S. moniliformis* infections observed in California over the past 8 years is attributable to these factors, the twofold increase suggests that this may be the case. Regardless of the reason for the increase, prevention of serious disease is dependent upon early clinical recognition, alerting the laboratory of the potential diagnosis, use of appropriate laboratory procedures, methods and media to recover and identify *S. moniliformis* from blood or other body fluids and tissues, and institution of appropriate antimicrobial therapy (penicillin, tetracycline).

Measures to decrease the number of RBF cases can be instituted. Extermination of rats in urban areas, where unintended exposure is highest, can be undertaken. People can be educated to avoid potentially contaminated food (including unpasteurized milk) and water. Finally, most laboratory infections can be avoided if laboratory workers are gloved and cautious when handling laboratory rodents (alive or dead).

REFERENCES