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A View on Rat Bite Fever

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ABSTRACT

Rat bite fever is caused by spirillum minus and streptobacillus moniliformis bacteria. It is transmitter to humans through contact with secretions or blood of an infected rodent. Rats are the most common carrier of the bacteria. Squirrels, gerbils, and other carnivores that prey on rodents can also carry the disease. The bacterium is transferred in approximately 10% of bites to humans. Both forms of bacteria primarily affect urban dwellers that live in crowded conditions. In the United States and Europe, most cases are caused by streptobacillus moniliformis and can be known as Haverhill fever or epidemic arthritic erythema.

1. INTRODUCTION

Rat bite fever was first discovered on February 18th 1926. The disease was first reported in the United States in 1839. An association with a specific pathogen was not reported until 1914, when Schottmüller described Streptothrix muris ratti, isolated from a rat-bitten man. This association was confirmed in the United States in 1916. In 1925, the organism was renamed Streptobacillus moniliformis, a name that has remained in general use since, although some reports refer to Actinomyces or Actinobacillus muris . A milk-associated outbreak of disease occurred in Haverhill, MA, in 1926 and was described by Place and Sutton. The organism found at this time was named Haverhillia multiformis by Parker and Hudson, although this most likely represents S. moniliformis disease. Any review of the literature regarding rat bite fever is complicated by the near-simultaneous description of Spirillum minus, the primary cause of rat bite fever in Asia, which is known by many as sodoku. Unfortunately, some reports discuss both organisms simultaneously, blurring the distinction between the two diseases and epidemiologic distributions that are, in fact, distinct.

2. MORPHOLOGY

Streptobacillus moniliformis is a highly pleomorphic, filamentous, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop characteristic lateral bulbar swellings. The organism is typically arranged in chains and loosely tangled clumps. It varies in its dimensions, from 0.1 to 0.5 µm by 2.0 to 5.0 µm, up to 10 to 15 µm, with long, curved segments up to 100 to 150 µm. S. moniliformis exists in two variant types, the normally occurring bacillary form and the inducible or spontaneously occurring, cell wall-deficient L form, growing with a "fried-egg" colony morphology. The L form is considered nonpathogenic; spontaneous conversion between the two forms in vitro has been reported and is felt by some to be

responsible for clinical relapses and resistance to therapy. Spirillum minus, the other etiologic agent of rat bite fever, was discovered during the 19th century and initially named Spirocheta morsus muris or Sporozoa muris. It was renamed Spirillum minus in 1924. The organism is a short, thick, gram-negative, tightly coiled spiral rod which measures 0.2 to 0.5 µm and has two to six helical turns. Because Spirillum minus cannot be cultured on synthetic media, initial diagnosis relies on direct visualization of characteristic spirochetes with Giemsa stain, Wright stain, or dark-field microscopy.

3. PATHOGENESIS

Because of the relatively low incidence and low mortality rate of rat bite fever when recognized and treated, little information describing the pathogenesis of S. moniliformis exists. However, the organism appears to be capable of producing morphological findings not customarily associated with bacterial infections. Autopsy of rat bite fever victims demonstrates pronounced erythrophagocytosis, hepatosplenomegaly, interstitial pneumonia, and lymph node sinus hyperplasia. Endocarditis and myocarditis have also been demonstrated, along with degenerative changes in the kidneys and liver. Radiological data suggest that rat bite fever may be considered a cause of damage to physes and acrophyses, mimicking frostbite damage, and clinical data suggest that S. moniliformis may have a predilection for synovial and serosal surfaces. Biopsy of skin lesions seen in rat bite fever has demonstrated leukocytoclastic vasculitis . Experimental infection in mice results in a progressive polyarthritis, beginning with fibrinopurulent exudate within the joint space and adjacent periostea in the first 24 h of infection. This changes to a predominately macrophage presence on day 4, followed by periarticular abscess and necrosis on day 7. Periostitis develops by 2 weeks and is followed by fibrous connective tissue proliferation after 3 weeks. The degree of polyarthritis depends on the size of the inoculum. It is of concern that persistence of organisms within joint spaces at 3 months of infection may occur despite the clearance of organisms from blood, liver, and spleen.

4. EPIDEMIOLOGY

More than 2 million animal bites occur each year in the United States, and rats are responsible for approximately 1% of these. Historically, the typical victim of rat bite fever was a child under 5 years old living in poverty, and over 50% of reported cases in the United States were children. Now that rats have become popular pets and study animals, the demographics of potential victims have broadened to include children, pet store workers, and laboratory technicians. Over 200 cases of rat bite fever have been documented in this country, but this represents a significant underestimate because neither the disease nor its causative organism is reportable to health departments. The youngest reported case of rat bite fever was in a 2-month-old infant, and the oldest reported case occurred in an 87-year-old man. The risk of infection after a rat bite appears to be 10% , and the mortality rate of untreated rat bite fever is approximately 13% .

5. GEOGRAPHIC DISTRIBUTION

Most reports of S. moniliformis originate from the United States, although other Western Hemisphere reports have come from Brazil, Canada, Mexico, and Paraguay. Most European reports come from the United Kingdom and France, but sporadic reports from Norway, Finland, Germany, Spain, Italy, Greece, Poland, Denmark, and The Netherlands also exist. Australia has also demonstrated some cases. Few reports from Africa exist, other than one report of sodoku from Kenya (8) and two episodes of squirrel bite-associated disease in Nigeria, probably underestimating the presence of S. moniliformis. Most reports from Asia document cases of sodoku, caused by Spirillum minus and not discussed here. Within the United States, most early reports originate from the eastern half of the country. However, S. moniliformis now appears to have migrated to the West Coast, and cases are documented nationwide.

The reported incidence of rat bite fever caused by S. moniliformis from laboratory rat bites is low. Of 65 cases of documented rat bite fever since 1938 that were reviewed for this article, only 8 (12%) were attributed to a laboratory rat exposure. This likely does not represent the true incidence of disease in humans because of low clinical suspicion by clinicians and the organism's strict growth requirements. Similarly, the incidence of wild-rat-associated disease is seriously underestimated, as not all cases of rat bite fever are associated with an actual bite. S. moniliformis may also be acquired by handling of the animal or by exposure to its excreta or saliva. Nineteen of the 65 reviewed cases (29%) documented no bite or known exposure, consistent with literature reports that 30% of patients report no known bite. However, as stated above, 10% to 100% of domestic rats and 50% to 100% of wild rats carry S. moniliformis, and a known bite causes infection approximately 10% of the time. Thus, rat bite fever and rat colonization with S. moniliformis represent a significant public health threat that remains unrecognized. Rat bite fever is associated with three clinical syndromes in the literature. Rat bite fever caused by S. moniliformis infection is the predominant form seen in the United States. Disease caused by Spirillum minus is known as sodoku and occurs primarily in Asia. Ingestion of S. moniliformis via contaminated food causes Haverhill fever, so named for the first description of an outbreak in Haverhill, MA.

6. INITIAL SYMPTOMS

S. moniliformis-associated rat bite fever is a systemic illness classically characterized by fever, rigors, and migratory polyarthralgias. After exposure, the incubation period ranges from 3 days to over 3 weeks but typically is less than 7 days. Many patients report symptoms suggestive of an upper respiratory tract infection during this time. If a bite has occurred, it typically heals quickly, with minimal residual inflammation and no significant regional lymphadenopathy. Persistence of significant induration at the bite site should suggest an alternate diagnosis, including sodoku. At disease onset, fevers begin abruptly and may range from 38.0°C to 41°C. Rigors associated with fevers are prominent. Fever may resolve in 3 to 5 days but can relapse. Other frequently reported symptoms in the initial phase of illness include headache, nausea, vomiting, sore throat, and severe myalgias.

7. DISEASE PROGRESSION

As rat bite fever progresses, over 50% of patients develop migratory polyarthralgias. The severity of pain and the presence of swelling and erythema indicate arthritis. Reports also document the presence of synovitis and nonsuppurative arthritis suggestive of rheumatoid arthritis. The joints involved include both large and small joints of the extremities. Many patients experience arthritis of at least the knee and ankle during their illness. Migratory polyarthralgia is the most persistent finding of rat bite fever, lasting several years in some patients. Nearly 75% of patients develop a rash that may appear maculopapular, petechial, or purpuric (20). Hemorrhagic vesicles may also develop on the peripheral extremities, especially the hands and feet, and are very tender to palpation. Appearance of this rash, especially the hemorrhagic vesicles, in the setting of an otherwise nonspecific set of disease signs and symptoms should strongly suggest the diagnosis of rat bite fever. The rash may persist beyond the other, more acute, symptoms. Approximately 20% of rashes desquamate, especially those with hemorrhagic vesicles.

8. CLINICAL FEATURES

Rat bite fever is associated with three clinical syndromes in the literature. Rat bite fever caused by S. moniliformis infection is the predominant form seen in the United States. Disease caused by Spirillum minus is known as sodoku and occurs primarily in Asia. Ingestion of S. moniliformis via contaminated food causes Haverhill fever, so named for the first description of an outbreak in Haverhill, MA.

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10. TREATMENT

Penicillin is the treatment of choice for proven or highly suspected cases of rat bite fever. Tests of S. moniliformis antibiotic susceptibility by the disk diffusion method usually demonstrate sensitivity to penicillins, cephalosporins, carbapenems, aztreonam, clindamycin, erythromycin, nitrofurantoin, bacitracin, tetracycline, teicoplanin, and vancomycin; intermediate susceptibility to aminoglycosides, fluoroquinolones, and chloramphenicol; and resistance to trimethoprim-sulfamethoxazole, polymyxin B, and nalidixic acid. Antibiotic susceptibility tests performed by broth macrodilution usually demonstrate the following MICs: penicillin, <0.03 μg/ml; cephalothin, <0.03 μg/ml; ceftriaxone, <0.03 μg/ml; vancomycin, 0.5 μg/ml; tetracycline, 0.25 μg/ml; erythromycin, 2 μg/ml; streptomycin, 8 μg/ml; and gentamicin, 1 μg/ml (68). Only one penicillin-resistant S. moniliformis strain has been demonstrated, and that was over 50 years ago. Adults with rat bite fever should receive 400,000 to 600,000 IU/day (240 to 360 mg) of intravenous penicillin G for at least 7 days, but this dose should be increased to 1.2 million IU/day (720 mg) if no response is seen within 2 days. Children should receive 20,000 to 50,000 IU/kg of body weight/day (12 to 30 mg/kg/day) of intravenous penicillin G for 5 to 7 days, followed by 7 days of oral penicillin V, 25 to 50 mg/kg/day (maximum, 3 g/day) divided four times per day. For penicillin-allergic patients, both streptomycin and tetracycline appear to be effective, but erythromycin use has been associated with treatment failures. Cephalosporins have also been used successfully and may be considered if cross-allergenicity with penicillin is felt to be unlikely. Other antimicrobials may be considered, based on the in vitro susceptibility data presented above, but no published evaluations of their effectiveness exist. Patients with S. moniliformis endocarditis require dual therapy with high-dose penicillin G in combination with streptomycin or gentamicin. The currently recommended dose for adults is 4.8 million IU/day (4.8 g) of intramuscular procaine penicillin G if the isolate is susceptible to 0.1 μg/ml. If the isolate is more resistant, 20 million IU/day (12 g) of intravenous penicillin G should be used for adults. Children should receive 160,000 to 240,000 IU/kg/day (96 to 144 mg/kg/day), up to the adult maximum of 20 million IU/day (12 g). Successful treatment of adults with a 4-week regimen has been demonstrated. The appropriate treatment length for children is not known, although 6-week regimens generally are considered effective for other causes of bacterial endocarditis. The use of streptomycin appears to enhance activity against the cell wall-deficient L forms of S. moniliformis ; one might anticipate that other aminoglycosides would provide the same benefit.

11. CONCLUSION

Rat bite fever, caused by S. moniliformis, is an under-recognized and under-reported disease characterized by abrupt onset of fever, rigors, and migratory polyarthralgias; it carries a mortality rate of approximately 10%. Although S. moniliformis is exquisitely susceptible to penicillin, most patients experience treatment delays due to the nonspecific nature of the clinical features, a broad differential diagnosis list, and difficulties in culture diagnosis. However, the changing epidemiology of rodent exposure, together with the risk of severe, invasive disease if left untreated, suggests that rat bite fever and S. moniliformis should occupy a more prominent place in our diagnostic thinking.

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