Forgotten diseases: Relapsing fever

I.T. GANGAIDZO

Introduction

Relapsing fever is a group of conditions that is characterized by recurrent febrile episodes interspaced with periods of no symptoms at all. They are arthropod-borne spirochetal infections of the *Borrellia* genus and occur in two main forms: tick-borne and louse-borne. Tick-borne relapsing fever is a zoonosis that is found worldwide. The louse-borne relapsing fever is caused by B. recurrentis, and is seen in the developing world. This form usually occurs in the setting of overcrowding. It is spread from person to person and can occur in epidemics, including large ones involving millions of people. Mortality rate may reach 40% when untreated, depending on host factors such as nutritional status and concurrent illness.

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Epidemiology and Pathophysiology

The human body louse and various ticks that infest rodents are the vectors that transmit spirochetal bacteria to humans. These organisms cannot be cultured in standard media, but (unlike the other spirochetes that cause human disease) they are easily identified at light microscopy using Wright's or Giemsa stains. Being members of the *Borrellia* spirochete genus, they measure 8 to 30 m in length. They are made up a helix with three to ten spirals.

The tick-borne variety is transmitted by more than 10 species of *Borrellia*. The ticks are the soft type of the genus *Ornithodoros*, and have a natural reservoir in rodents and small mammals that reside in warm areas at altitudes of 450 to 2800 meters. The ticks, which have a painless bite, usually feed at night for five to 20 minutes. As a result, exposure to the vector may go unnoticed. Most cases are acquired in shrubs and forests.

A single *borrelia* spirochete may produce 30 different variants or serotype progeny during the same infection. This happens as a result of the spirochete's ability to reconfigure its outer membrane antigens, in association with the human immune response and resulting in the characteristic episode of fever interspersed with asymptomatic periods. Each surface antigen is activated genetically in order to evade the human's serospecific antibody response. As the first serotype wanes and the fever subsides as a result of an effective antibody response by the host, another antigen is expressed by a new bacterial variant. Another febrile episode ensues as this new serotype multiplies, necessitating a new antibody response. This immunologic cycle of events is responsible for the periodicity of symptoms that is characteristic of the disease.

Clinical Manifestations

Relapsing fever presents with a sudden onset of fever, punctuated by an intervening afebrile period, with the pattern occurring at least twice. The temperature may be as high as 43°C and is usually above 39°C. The acute clinical period lasts a few days then terminates as abruptly as it began. In louse-borne relapsing fever, the first episode of fever is unremitting for three to six days, and it is typically followed by a single milder episode. In tick-borne relapsing fever, there are multiple febrile periods that last from one to three days each, and may last for several weeks. In both forms, the interval between fevers ranges from three days to two weeks.

The first fever episode ends by crisis, consisting of rigors, a further elevation in temperature. There is a rise in pulse rate and blood pressure, lasting approximately 20 minutes. The crisis phase is followed by profuse sweating, a fall in temperature, and hypotension which usually persists for several hours. Mortality from untreated relapsing fever is most common during the crisis or the period that soon follows it.

There are many non-specific symptoms that may accompany the fever. Headache, neck stiffness, arthralgia, myalgia, and nausea may occur. In addition, there may be dizziness and unsteadiness of gait. A nonproductive cough

Department of Medicine
University of Zimbabwe
P O Box A178
College of Medicine
Harare, Zimbabwe

is common during louse-borne relapsing fever and may raise a suspicion of influenza in this particular clinical setting. Neurologic manifestations include delirium or apathy, occasionally stupor or coma, facial palsy, myelitis, and radiculopathy. These are more common in tick-borne relapsing fever than louse-borne relapsing fever. Although the first episode of illness tends to be the most severe, some complications, particularly neurologic ones, are more common during subsequent febrile periods.

Epistaxis, petechiae, and ecchymoses are common findings on physical examination during louse-borne relapsing fever but not tick-borne relapsing fever. The bleeding disorder is probably the consequence of thrombocytopenia, impaired hepatic production of clotting factors, and/or blockage of small vessels by aggregates of spirochetes, erythrocytes, and platelets. Splenomegaly is also common. The majority of patients with louse-borne relapsing fever and about 10 percent of patients with tick-borne relapsing fever have enlarged livers.

Myocarditis appears to be common in both louse-borne and tick-borne relapsing fever, although it is often undetected on routine evaluation. Heart involvement has been prominent in fatal cases. The most common evidence of myocarditis is the presence of a gallop rhythm on cardiac auscultation. While patients frequently complain of polyarthralgia, enlarged, painful joints are unusual.

Neurologic findings are more common in tick-borne than louse-borne relapsing fever and are due to direct invasion of spirochetes. Meningitis or meningoencephalitis is serious consequences of this invasion that can result in residual hemiplegia or aphasia. Unilateral or bilateral Bell's palsy or deafness from seventh or eighth cranial nerve involvement are the most common forms of cranial neuritis in tick-borne relapsing fever; if it occurs, cranial neuritis typically presents in the second or third febrile episode, not the first. Visual impairment from unilateral or bilateral iridocyclitis or panophthalmitis may be permanent.

In louse-borne relapsing fever, neurologic manifestations such as altered mental state or stiff neck are thought to be secondary to the spirochetemia rather than direct invasion of organisms into the central nervous system. Subarachnoid hemorrhage has been observed, and may be a result of disseminated intravascular coagulation.

Routine laboratory studies are not specific in relapsing fever. A mild to moderate normocytic anemia is common. Leukocyte counts are usually in the normal range or only slightly elevated, and there can be leukopenia during the crisis. Platelet counts can fall below 50,000/mm3. There is no evidence of haemolysis. Evidence of hepatitis can occur with elevated serum concentrations of unconjugated bilirubin and aminotransferases; the prothrombin and partial thromboplastin times may be moderately prolonged. Hypoalbuminemia can occur but is more often due to malnutrition than hepatic dysfunction.

Some patients have a prolonged QTc interval because of myocarditis. Some such patients may have cardiomegaly and pulmonary edema on chest radiograph.

Lumber puncture and analysis of the cerebrospinal fluid (CSF) is indicated in cases with signs of meningitis or meningoencephalitis. The findings usually exclude bacterial and most other non-viral infectious causes of meningitis. A mononuclear pleocytosis and/or mildly to moderately elevated protein levels in the CSF provides justification for intravenous antibiotic therapy in patients with tick-borne relapsing fever. Typically, glucose concentrations in the CSF are usually not depressed.

The most useful laboratory investigation is thin and thick smears of blood. Giemsa or Wright stains typically reveal the spirochetes in a methanol-fixed thin smear if the concentration of microorganisms is greater than 105 per mL. Up to 200 oil immersion fields should be viewed before judging the smear to be negative. The optimum time to obtain blood is between the fever's onset and its peak. Once the temperature is declining or is back to the normal range in the absence of antipyretics, spirochetes usually cannot be visualized in blood.

A further increase in sensitivity can be achieved by centrifugation of heparinized or citrated blood followed by examination of the buffy coat and overlying plasma. Another diagnostic maneuver is the wet mounts. Uncentrifuged plasma or the concentrated buffy coat are examined by phase contrast or dark field microscopy for motile spirochetes. The wet mount is prepared by merging one drop of citrated or heparinized blood with one drop of normal saline or phosphate-buffered saline under a cover slip. All of these direct visualization methods facilitate diagnosis. A smear or wet mount properly evaluated can be diagnostic since *Borrellia* sp are an unlikely contaminant and an asymptomatic carrier state is not known to occur. In less experienced hands, however, stain artifacts in blood smears and incorrect interpretation of wet-mounts may produce false diagnoses.

When relapsing fever is suspected but spirochetes are not directly visualized by the above techniques, laboratory confirmation of the clinical diagnosis requires techniques that are not available in most laboratories, namely animal inoculation and in vitro cultivation. In vitro cultivation is an alternative to animal inoculation for demonstrating the organism in blood. Kelly's medium and its most commonly used derivative, Barbour-Stoenner-Kelly (BSK) medium, supports the growth of most *Borrellia* spp.

Direct or indirect immunofluorescence is another procedure that can be used with thick or thin smears to visualize spirochetes. Fluorescein-labeled polyclonal antibody to *Borrellia* burgdorferi is commercially available and has sufficient cross-reactivity with other *Borrellia* spp. to be useful for detecting relapsing fever spirochetes in the blood or in tissues. There is little reported experience with the use of polymerase chain reaction for the diagnosis of human relapsing fever

Differential diagnosis.

Several conditions can mimic relapsing fever, and other illnesses may accompany the louse-borne form. The soft

ticks are not known to transmit other infections to humans. However, under the conditions the same conditions that promote epidemics of louse-borne diseases, patients can also acquire epidemic typhus, typhoid, measles, tuberculosis, or malaria.

Depending on the history of travel, residential, occupational, and recreational exposures, the differential diagnosis of relapsing fever includes one or more of the following infections:

Malaria, Babesiosis, Influenza, Typhoid fever, Tularemia, Brucellosis, Rickettsioses, Dengue, Leptospirosis, Rat-bite fever, Meningococcemia and Viral hepatitis.

Clinical course

The mortality rates for untreated louse-borne relapsing fever is 10 to 70 percent, while that for tick-borne relapsing fever is in the range 4 to 10 percent, respectively. Prompt administration of appropriate antibiotics results in a reduction in death rate for louse-borne relapsing fever to 2 - 5 percent and for tick-borne relapsing fever to less than 2 percent. Poorer prognostic features include: Stupor or coma on admission, diffuse bleeding, myocarditis, hepatic dysfunction, bronchopneumonia as well as co-infection with typhus, typhoid, or malaria

Treatment

Oral doxycycline or tetracycline is the drug of choice. Pregnant women and children can receive erythromycin. A single 500 mg dose of tetracycline or erythromycin is usually sufficient for louse-borne relapsing fever. Owing to the high rate of treatment failure in the tick-borne variety, a seven to ten day course of the same drugs is necessary. Central nervous system involvement should be managed with ceftriaxone or penicillin (or chloramphenicol). The Jarisch-Herxheimer reaction may occur within three hours of giving treatment. It is characterized by fever, rigors and hypotension.It may last for 24 hours and treatment is supportive. The reaction may lead to a mortality rate in louse-borne relapsing fever of approximately 5 percent. Some patients have survived the crisis or Jarisch-Herxheimer reaction, only to die suddenly later that day or the next, perhaps from an arrhythmia.

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