Relapsing fever

Summary

- Spiral shaped bacteria, transmitted by ticks (endemic) or lice (epidemic)
- Recurrent fever, rash, hepatosplenomegaly, red eyes, haemorrhagic diathesis, muscular pain, coughing, confusion, neurological complications
- Thick film test positive, esp. in beginning of attack
- Treatment with penicillin or tetracyclines (e.g. doxycycline)

General

Borrelia sp. are very thin, spiral shaped bacteria. They are **larger, longer and have looser coils** than treponemes or leptospires. They are responsible for major diseases, including **recurrent or relapsing fever**. In 1868 the German Otto Obermeier identified the microorganisms during an epidemic in Berlin. The pathogenic potential was demonstrated in 1874 by Gregor Münch, who inoculated himself with *Borrelia recurrentis* and survived the subsequent relapsing fever. The French microbiologists Sergent and Foley identified the body louse as the vector. The British pathologist Joseph Dutton (famous because of *B. duttoni*) discovered an alternative vector: the Argasid soft tick *Ornithodoros moubata*. He injured himself while performing an autopsy on a patient who had died from borreliosis and died himself from relapsing fever. During his research into East Coast fever in East Africa, Robert Koch discovered that transovarial transmission took place in these ticks. Charles Nicolle and co-workers established that *Borrelia recurrentis* disappeared from the intestine of the louse 24 hours after a blood-meal, to appear again suddenly in the haemolymph of the insect after 6-8 days. Experimental animals such as rats and mice can be inoculated successfully. *Borrelia recurrentis* can be grown in chicken embryos and since 1994 in-vitro.

There are two types of borreliosis: relapsing fever, **louse-borne borreliosis (*Borrelia recurrentis*)** and **tick-borne borreliosis** (***Borrelia duttoni*** and many other varieties, depending on the geographical region). The bacteria are morphologically identical. The name “tick-borne borreliosis” sometimes causes confusion, as *Borrelia burgdorferi* is also transmitted by ticks, but this organism does not cause relapsing fever.

Epidemic, louse-borne relapsing fever

In the **epidemic** form of borreliosis the bacterium ***Borrelia recurrentis* is transmitted by lice**. The vector is the common body louse (*Pediculus humanus corporis*). [The body louse is also the vector of epidemic typhus and of *Bartonella quintana*. This insect is not to be confused with the pubic louse (Phthirus pubis)]. The head louse (*P. h. capitis*) hardly ever plays a part in transmission. There is no transovarial transmission of *Borrelia recurrentis* in the louse. **Humans are the reservoir** of the disease.

The louse is infected by sucking blood at the time the patient has an outbreak of fever. At this time the levels of bacteria in the blood are at their highest. The bacteria penetrate the insect's intestine and multiply in the haemolymph ["blood"] of the louse. The bacteria do not penetrate the salivary glands. The disease is not transmitted by the bite itself. **If an infected louse is crushed on the skin when scratching, the bacteria can penetrate into the skin**. Lice do not like high temperatures and will readily leave a person who has a fever. In the event of poor hygiene and close physical contact between people lice can pass from a sick person to a healthy person

The disease is **rare but can occur all over the world**. The geographical distribution of LBRF has declined due to improvements in living standards. Currently the disease is primarily found in limited endemic foci in Ethiopia but also in Somalia and Sudan. The disease has also been recorded in the rural Andean community in Peru and in northern China. Epidemics occur in conditions of poor hygiene, overcrowding and malnutrition, such as in floods, mass migration, earthquakes, concentration camps and refugee camps, war, and in the slum districts of large towns. Body lice multiply rapidly and a population can increase by 11% per day. Infection is more frequent in the cold months. People live closer together then, wear more clothes, so there are more lice and consequently more transmission. **Mortality can be very high (30 to 80%).** Between 1910 and 1945 there were 7 large epidemics in Africa, Eastern Europe and Russia with 15 million cases and 5 million dead.

Endemic, tick-borne relapsing fever

This is a sporadic, endemic disease in a number of areas caused by *Borrelia duttoni* and related bacteria. The vectors are **soft ticks** (*Ornithodoros sp.*). In West Africa *O. erraticus* is

responsible for the transmission of *B. hispanica*. In Central, Eastern and Southern Africa *Ornithodoros moubata* is the main vector (*B. duttoni*). These latter ticks infect people through their saliva and through coxal fluid. It is mainly an infection of rodents. These animals are the principal reservoir. Because the bacterium in ticks passes from one generation to the next by transovarial transmission, the ticks themselves also form a reservoir. People can be infected by ticks for example when walking through grass or bushes. In Central Africa there is a domestic variety whereby the ticks live in cracks in the walls of mud huts and are therefore more likely to bite humans. The people who are infected are then the main reservoir. Ticks can live for a number of years (exceptionally up to 15 years) unlike lice (a maximum of 2 months). They can survive for a long time without a blood-meal. **Mortality in man is lower with tick-borne borreliosis (2 to 5%) than with the epidemic form**. The local population builds up immunity from repeated infections; they usually have a mild form. The bacteria can cross the placenta to the fetus.

Over the course of an infection in a single human host *Borrelia sp*. regularly display **antigenic variation**, mainly by changing various surface proteins ("variable large proteins and variable small proteins").

Clinical Aspects

After an incubation period **of 4 to 14 days (1 week on average),** the patient suddenly develops a **violent fever** (39° to 41°C). This is accompanied by a **high bacteraemia**: $10^{6\text{-}8}$/ml. The concentration of bacteria is so high that they can be detected with the **thick film test or a thin blood smear** (in classical Gram-negative bacteraemia (e.g. *E. coli*) the concentration of bacteria is much lower). The patient suffers from headache, muscular pain and pain in the joints. There is often a dry cough and dyspnoea, which can be quite severe. The patient sometimes suffers from abdominal pain and diarrhoea. The patient is frequently jaundiced. The spleen, the liver and the lymph nodes are often swollen. Neurological abnormalities occur. The conjunctivae are often red. Sometimes (in 4 to 50% of cases) there is a discrete rash which usually appears when the first fever peak subsides. Diffuse intravascular coagulation (DIC) and thrombocytopenia, petechiae and haemorrhaging can occur, e.g. epistaxis (nose bleeds). Sometimes (1/3) a considerable leucocytosis can be present, but leukopenia can also occur. The cerebrospinal fluid can contain an increased number of lymphocytes (mainly in endemic tick-borne borreliosis). The fever suddenly

disappears after 2 to 8 days on average 5 days. This is usually accompanied by an aggravation of the symptoms, hypotension and sometimes death. The prognosis is worse with louse-borne borreliosis, when there is manifest jaundice, hypotension and high bacteraemia (which can be objectivised in a thin blood smear). There is high neonatal mortality (50%).

The first febrile episode is followed by a period **of 3 to 30 days (on average 9 days) without fever**. In 60% of patients this is followed by a second febrile period, which is somewhat less severe than the first and also lasts for a shorter time (on average 2 days). This can be repeated a number of times: maximum 4 times in case of louse-borne borreliosis, maximum 11 times in case of tick-borne borreliosis. This characteristic explains why it is called “relapsing fever”.

Complications are meningo-encephalitis with as sequelae facial paralysis, deafness and paralysis of the eye muscles (mainly endemic tick-borne borreliosis). Most spirochaetes are neurotropic. Myocarditis and abortion may also occur. If a pregnant woman has relapsing fever she has around a 50% risk of going into labour.

Diagnosis

The clinical **signs and symptoms are not specific** apart from the **recurrent bouts of fever**. At the beginning of a febrile episode bacteria are found in the blood. These very thin spiral shaped bacteria (0.5µm) can be seen in an unstained unfixed preparation because of their typical mobility. They can also be stained with Giemsa and Wright stain. Staining with Diff-Quik (xanthene thiazine stain) is an alternative. They are found between the red blood cells. The fact that the bacteria can be seen in peripheral blood is explained by the very high density of the bacteria. *Borrelia* spp can be cultured through animal inoculation or in vitro cultivation in a Barbour-Stoenner-Kelly (BSK) medium. PCR and serology are only available in a few reference laboratories.

The differential diagnosis includes **many febrile conditions** including malaria, typhoid fever, hepatitis, amoebic hepatic abscess, leptospirosis, rat bite fever, septicaemia, arbovirosis, ehrlichiosis and anaplasmosis, babesiosis, rickettsial diseases (can also be transmitted by lice and ticks).

Treatment

Tetracyclines are the first choice, e.g. doxycycline. A single administration is often sufficient. Alternatively erythromycin can be given. In the case of louse-borne borreliosis, in ± 90% of patients a spectacular deterioration in the symptoms is seen 1 to 3 hours after starting therapy: headache and muscular pain, tremor, very high fever, tachypnoea, tachycardia and initial hypertension. This is followed shortly after by excessive perspiration and hypotension and sometimes shock. This is a so-called **"Jarisch-Herxheimer"** reaction which usually lasts 6 to 12 hours. This reaction rarely occurs (1%) with tick-borne borreliosis. The reaction was first described in syphilis patients who were being treated with mercury chloride or penicillin. It can also occur when treating other infections caused by intracellular bacteria (such as Brucella, Q fever). It has a mortality rate of about 5%. It is thought that it develops from various substances being released from the destroyed bacteria, together with high concentrations of certain cytokines (e.g. TNF alpha, IL-6 and IL-8). Steroids are not effective in preventing the reaction. It has been shown that treatment with anti-tumour necrosis-alpha antibodies mitigates the Herxheimer reaction. The patient must be kept under close supervision (bed rest, IV infusion). Penicillin is less frequently associated with Herxheimer reactions but is less effective (often further recurrences).

Prevention

There is no vaccination and no lasting immunity after a patient has had the infection. In the case of an epidemic (louse-borne borreliosis) mass delousing is often carried out (2 x with an interval of 2 weeks) for example in refugee camps. This is based on the use of insecticides and hot sterilisation (boiling and washing) of clothes.

Borrelia vincenti

It is not clear whether this bacterium is itself a pathogen or whether it is present as a saprophyte in necrotic material. The bacteria can, unlike the other *Borrelia* be cultured in an anaerobic environment. In combination with certain anaerobic bacteria (fusobacteria = anaerobic Gram-negative "fusiform bacteria") this bacterium is suspected of causing ulcerative damage in the:

- **throat**: *Plaut-Vincent's angina.* This results in a major throat infection with localised necrosis. DDx: diphtheria of the throat, local anthrax or plague.
- **gums**: *Trench mouth or Vincent's stomatitis*, a necrotising and ulcerative gingivitis of the cheek. This occurs in malnourished children and sometimes after herpes simplex.
- **cheeks / lips**: *Cancrum oris (noma)* is characterised by pain and extensive tissue destruction. Treatment consists of penicillin, correct nutrition and treatment of any underlying disorder (e.g. kala-azar, etc). Plastic surgery will be needed.
- **scrotum**: Gangrene of the scrotum (*Fournier's gangrene*).
- **skin**: Painful (in the acute stage), purulent, foul-smelling ulcers, mainly on the legs or feet (*phagedenic or tropical ulcer*). Ulcers such as this can drag on for years or sometimes heal spontaneously. In some patients a spinocellular carcinoma develops which is invasive locally and can metastasise to the local lymph nodes. Treatment consists of penicillin and metronidazole. Local wound cleaning, antiseptics and non-adhesive dressings are important. Dry dressings should be avoided because they prevent the forming of new epithelium (when the dressing is removed the new cells are pulled off).