Malaria from Ticks – Babesiosis

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In Europe the hard tick *Ixodes ricinus* is the vector of 5 human diseases: tick-borne encephalitis (TBE), Lyme borreliosis, tularaemia, anaplasmosis, and babesiosis. The tick can transmit the microbes of these diseases to humans when sucking blood.

The rarest of these diseases is babesiosis, which exists in Finland (1). Symptoms of babesiosis can be similar to those of granulocytic anaplasmosis. First and foremost, however, it should be noted that babesiosis can mimic malaria. This is unsurprising, since, as in malaria, the vector is a protozoan, an intraerythrocytic parasite.

Babesiosis is a great infector of cattle, although lambs and dogs can also be infected. Vets are often familiar with this disease (2). However, from contacts in Finland, my experience of their know-how has proved disappointing. This lack of knowledge also applies to ehrlichiosis and borreliosis, and their vectors, the ticks, which globally seems to be the Achilles heel for many.

Skin symptoms are absent in babesiosis. If skin symptoms occur, they may have been caused by the treatment, that is similar to that in malaria. Rashes are also rare in human anaplasmosis (HGA), while they dominate in borreliosis. Authors from New England in north-eastern USA (3) report that babesiosis should be considered in all patients who have an inexplicable feverish disease and have lived in or travelled to an area where the disease is endemic. The disease must also be kept in mind when examining people who have received a blood transfusion within the past 6 months. Transfusion-transmitted babesiosis (TTB) is a major problem, which has not been sufficiently investigated in Europe (4).

History of babesiosis

In 1888 Victor Babes, a Hungarian pathologist and microbiologist, observed intraerythrocytic microorganisms in feverish cattle with bloody urine (5). Five years later Smith & Kilborne from the USA (6) observed that ticks were vectors of *Babesia bigemina* in Texan cattle. Thus, for the first time, it was demonstrated that an arthropod (tick) could contract a microbe to a vertebrate host. However, Babes' idea of bacteria was not correct (5).

The first case of human babesiosis was reported half a century later, when a Croatian shepherd, whose spleen had been removed, rapidly succumbed to a disease caused by *B. divergens*. The first case in a healthy (immunocompetent) person was observed in the USA, on Nantucket Island, in 1969. The disease was caused by *B. microti* and the tick vector was *I. scapularis*. New cases appeared on the island and the disease was named Nantucket fever. Human infection with *B. microti* is almost as common as Lyme disease (borreliosis) in some areas of New England (3).

Prevalence of babesiosis in Europe

Until publication of my Finnish article in 2014 (7), there was evidence of approximately 50 persons in Europe with clinical symptoms of babesiosis; most of them caused by *B. divergens*. A little surprisingly, more than half of these 50 persons are from France and the British Isles (4). The disease is evidently very rare, but as it is poorly known in Europe many cases may occur without correct diagnosis (8). Only two cases of human babesiosis have been described in Russia, both caused by *B. microti* (4).

The microbe, piroplasm

B. microti is the cause of babesiosis in the USA, whereas in Europe the cause is mainly *B. divergens*. *B. microti* does not exist in the larvae of ticks, nor do the respective microorganisms of anaplasmosis and borreliosis. However, *B. divergens* can be found in this first stage of *I. ricinus*, and consequently in all 3 stages of sucking blood: larvae, nymphs and adult female ticks (4).

Another question is which are the reservoir hosts; vertebrates "giving" ticks their blood meal and having living piroplasms in their blood? To my astonishment I omitted to write about that in my Finnish article (7). The explanation is that there was no comment regarding these (reservoirs) in the many reviews and other articles I read. Thus, work remains to be done!

Frequency of the protozoan in the tick

The reported infection prevalence varies from 0.9% to 20%; evidently this has not been sufficiently investigated by medi-

cal entomologists. It is not reported (4) how these percentage prevalences are measured: in nymphs, also the main vectors in this disease, or in adult female ticks? Nymphs are less infected than adult females. And what about the larvae? Can more than one human pathogenic microbe occur in a single tick? Differences of opinion exist regarding this question (4). More likely is that one tick has one microbe of the diseases mentioned at the start of this article, and another tick another, and so on. Simultaneous infections, as in the Finnish case report (1), with *Babesia* and *Borrelia*, are possible, but probably from separate ticks. In cases of simultaneous clinical borreliosis (1) or some other tick-borne disease the patient has more prominent and longer-lasting symptoms.

Incubation time

The incubation time is 5–33 days after the tick has attached (4). A review article from the USA reported 1–4 weeks after the infection of *B. microti* and [sic]! 1–9 weeks, sometimes even months, if the pathogen is contracted via blood transfusion (TTB) (3). In the USA more than 160 cases of blood transfusion babesioses have been detected. Because the problem is severe the question of how to allow blood donation without "donating babesia" must be considered (9).

Reporting of cases

Babesiosis, as with ehrlichioses and borreliosis, are diseases to be reported to the US authorities, which is not the case in Europe. In Finland, veterinarians must report new cases to the Ministry of Agriculture and Forestry (1). Although cattle babesiosis is endemic in Finland, infections have greatly reduced over the period 1965–2004. This seems very odd, and raises the question as to the reasons for this: nothing similar has been observed in Europe (4) or in the USA (3).

Clinical symptoms

The symptoms of babesiosis are fever, chills, headache, myalgia, sometimes joint pain, dry cough and nausea. Flu-like symptoms may also be present, as seen in anaplasmosis. Fever is the dominating symptom. Usually the urine appears very dark, and in severe infections haemoglobinuria occurs (4). "Acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulopathy are the most common complications…" (3, 10).

The protozoan can affect persons from childhood, but usually affects people in the age range 40–60 years.

Immunity

Is it possible to be infected more than once? I could not find an answer to this question, despite reading many reviews and other articles.

Laboratory diagnosis

Changes in hemolytic anemia for hemolytic disorders are low levels of haemoglobin and haematocrit (B-HKR), a normocytic anaemia, often thrombocytopaenia but rarely leucopaenia (3,

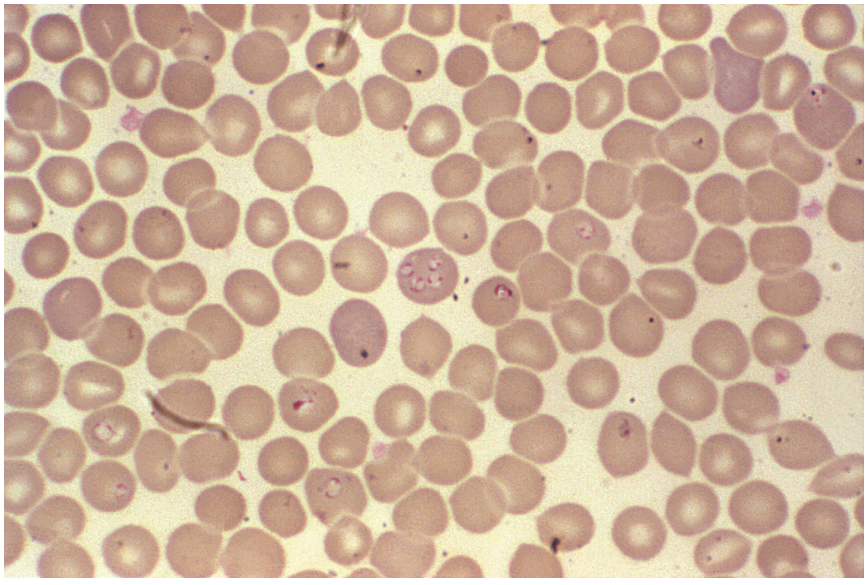

Fig. 1. Microscopy of a blood smear in which intraerythrocytic *Babesia* prozoans are visible. Published with permission from Skinfo (7).

4). The duration of the disease is usually 1–2 weeks, but fatigue can last for months (3).

Microscopic findings

The final diagnosis of babesiosis is usually made from examination of thin smears of blood stained using the Giemsa or Wright method (Fig. 1). It is possible using this technique to separate *B. microti* and *B. divergens* infections from each other and further from malaria. PCR is an important complementary investigation, as in anaplasmosis (HGA).

A curiosity that may be seen in blood smears is the so-called Maltese cross (Figs 2 and 3). This is seldom recognized, but pathognomonic to babesiosis caused by *B. microti* or *B. duncani* (3). The Finns reported this cross of the protozoan in their *B. divergens* patient (1).

Of course, the real Maltese cross with its special geometry is impossible to reproduce biologically. This is seen in the fine portrait of Michelangelo Merisi, more commonly known as Caravaggio; my favourite painter (Fig. 3). There are two portraits painted by him of the Grand Master of the Order, Alof de Wignacourt: one full figure, showing the master in armor and accompanied by a page, now in the Louvre; and then this (Fig. 3). Both produced in Malta (13).

Malaria

Malaria is the primary differential diagnostic disease. Malaria existed in Finland 100 years ago, spread by the malaria mosquito. When cowsheds were separated from human homes and swamps were dried malaria gradually disappeared from Finland and other Nordic countries, for example Sweden. This subject has (long ago) been discussed in Nordic dermatological meetings. The malaria mosquito may still exist, but without the protozoan. "Malaria can be eliminated from consideration on the basis of a travel history and a careful review of blood smears (3)".

Treatment of babesiosis

B. divergens (Europe) and mild disease: clindamycin. Severe disease: clindamycin and quinine.

B. microti (USA) and mild disease: atovaquone and azithromycin. Severe disease: clindamycin and quinine (4). quinine is not tolerated by all patients, but is not absolute necessary. The duration of treatment is short: usually 7–10 days.

Blood transfusions are recommended in all cases of severe infection with *B. divergens*, because we have no knowledge of exo-erythrocytic stages of *B. divergens*. Thus, the elimination of parasitic erythrocytes (the activation of the spleen) appears to be beneficial. At the same time the anaemia will be cured. Persons who have had their spleen removed are a risk group when infected, as in the first and fatal case reported in humans.

The severity of babesiosis depends on the patient's immune response and the species of *Babesia* causing the infection (3). In persons with normal health the disease is seldom severe. Persons over 50 years of age are reported to be at risk (3)! The

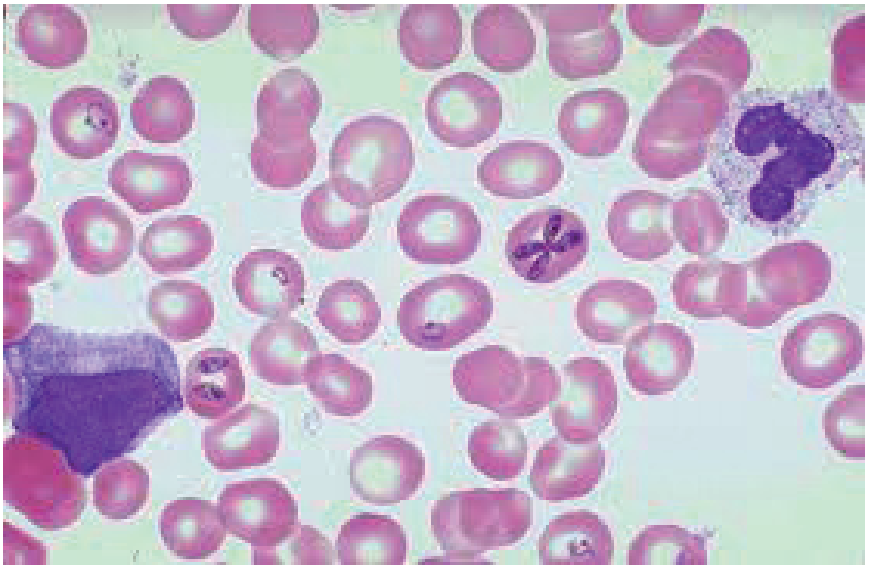

Fig. 2. Blood smear in which the pathognomonic Maltese cross in an erythrocyte is visible in the centre of the figure. Published with permission from Alexander Salava.

Fig. 3. Caravaggio, portrait of Alof de Wignacourt, size 144×95 cm, Florence, Palazzo Pitti. The large white Maltese cross on a black background. Published with permission from Skinfo (7).

authors justify this astonishing statement by reporting that the immune response slowly weakens in people over 50 years of age (3). How many doctors in Finland and other Nordic countries are then in the risk group? One-third?

Ticks, the vectors of babesiosis

The majority of ticks spreading babesiosis are hard ticks (family *Ixodidae*), but because of the almost global prevalence of this disease soft ticks (family *Argasidae*) are also vectors (11).

When considering an infection it is important to understand some basic facts about ticks (*I. ricinus*, and evidently also *I. persulcatus* in Europe). When and where are they waiting for their prey? These ticks are near us, rather than far away in the woods. Dumler & Walker, in my ehrlichiosis-article (12), state that: "most infections occur within hundred yards from home". Here in Finland Ixodes ricinus may be active from early spring to late autumn; a mean temperature of +5°C 24 hours a day is sufficient. Thus, for approximately 6 months of the year an infection is possible in middle Finland, for example here in North Karelia.

Conclusion

In cases of flu-like high-feverish symptoms granulocytic anaplasmosis and babesiosis must be considered. The activity time of ticks (according to meteorology) must be taken into account. A restricted blood count including thrombocytes is an important and cheap investigation. The ABC of ticks must be managed. Both of these diseases have a precise treatment, although they usually resolve spontaneously. Concerning prevalence, I refer to my article about ehrlichioses in *Forum for Nordic Dermato-Venereology* (12).

I have discussed babesiosis with two Finnish vets and one from the USA (California). Comments from the New World were especially welcome. Unfortunately, rare diseases, such as babesiosis, risk being forgotten. However, it is also the case that babesiosis is a fascinating disease!

References

1. Haapasalo K, Suomalainen P, Sukura A, Siikamäki H, Jokiranta TS. Fatal babesiosis in man, Finland, 2004. Emerg Infect Dis 2010; 16: 1116–1118.
2. Mosqueda J, Olvera-Ramirez A, Aguilar-Tipacamu G, Canto GJ. Current advances in detection and treatment of babesiosis. Curr Med Chem 2012; 19: 1504–1518.
3. Vannier E, Krause PJ. Human babesiosis. N Engl J Med 2012; 366: 2397–2407.
4. Hildebrandt A, Gray JS, Hunfeld K-P. Human babesiosis in Europe: what clinicians need to know. Infection 2013; 41: 1057–1072.
5. Babes V. Sur l'hemoglobinurie bacterienne du boeuf. C R Acad Sci 1888; 107: 692–694.
6. Smith T, Kilborne FL. Investigations into the nature, causation, and prevention of Texas or southern cattle fever. Department of Agriculture Bureau of Animal Industry bulletin no. 1. Washington, DC: Government Printing Office, 1893; 177–304.
7. Uggeldahl P-E. Puutiaismalaria – babesioosi. Skinfo 2014; 41: 8–12 (in Finnish).
8. Hildebrandt A, Hunfeld K-P. Humane Babesiose- eine seltene, aber potenziell gefährliche Zoonose. Dtsch Med Wochenschr 2014; 139: 957–962.
9. Simon MS, Leff JA, Pandya A, Cushing M, Shaz BH, Calfee DP, et al. Cost-effectiveness of blood donor screening for Babesia microti in endemic regions of the United States. Transfusion 2014; 54: 889–899.
10. Panduranga V, Kumar A. Severe babesiosis presenting as acute respiratory distress syndrome in an immunocompetent patient. Conn Med 2014; 78: 289–291.
11. Gray J, Zintl A, Hildebrandt A, Hunfeld K-P, Weiss L. Zoonotic babesiosis: overview of the disease and novel aspects of pathogen identity. Ticks and Tick Borne Dis 2010; 1: 3–10.
12. Uggeldahl P-E. Doxycycline deficiency synrome: Ehrlichiosis. Forum for Nord Derm Venereol 2017; 22: 13–15.
13. Bonsanti G: Caravaggio. The Library of Great Masters. Scala Riverside, Riverside Book Company, Inc., New York, 1984.