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Review paper

Tick-Transmitted Diseases Caused by Apicomplexa

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Summary. The objective of this study is to draw attention to Apicomplexa-caused diseases transmitted by ticks. We present ultimate and intermediate hosts of Apicomplexa, including man, as well as vectors transmitting these unicellular Protista. We describe symptoms of Apicomplexa-caused diseases and contemporary methods of diagnostics and therapy. It is noteworthy that the ticks and tick-transmitted pathogenes are distinctly increasing their distribution ranges. Besides, it is important that the ticks are adapted to use many different hosts, including birds, which increases the ticks' expansion abilities.

Key words: Apicomplexa, *Babesia*, *Hemolivia*, *Hepatozoon*, *Theileria*, ticks.

1. INTRODUCTION

There are many reasons for complex studies on ticks: their ecology, physiology, biochemistry and many other aspects. Though it is commonly believed that ticks live mainly in forests, they can be found in typical synanthropic habitats including city parks, green squares and recreational places (Buelvas *et al.* 2008, Cieniuch *et al.* 2009, Reye *et al.* 2010). The situation is a result of man's tendency to seek contact with nature and of the common animal farming. This may be the reason for ticks migration from woodland areas to closely synanthropic habitats. The mite transport to man's immediate surroundings can be effected through dogs or other domestic animals, and also through people who are accidental hosts to various tick species.

Ticks are distributed world-wide. Depending on the climatic zone, some habitats harbour potential hosts, reservoir species and various tick species which can be vectors to some microorganisms. The state of stablilised coexistence may become disturbed by man in various ecosystems, for example through introducing domestic animals into biocoenoses. The reasons for dispersal of ticks and tick-transmitted microorganisms can vary. Ticks are very expansive also because they are able to feed on various hosts, including birds which transport them over long distances (Siuda 1993).

It is commonly accepted that ticks evolved on the boundary of the Paleozoic and Mesozoic as blood-

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sucking mites, parasitizing vertebrates. From the start they were blood-drinking mites, parasites of vertebrates (Hoogstraal 1985, Oliver 1989). Their long ectoparasitic career predisposes them to become vectors of many microorganisms. In the course of coevolution of ticks and their hosts, many possibilities of horizontal and vertical transport of microorganisms arose: transport between individuals and generations of ticks, as well as many adaptations enabling the microorganisms to travel from their vectors to their vertebrate hosts.

Hard ticks can spread ethiological agents of various diseases. Besides those which are described the most often: spirochaetes causing borreliosis, the disease widespread among humans of northern hemisphere (Bilski 2009, Buczek *et al.* 2009), viruses, representatives of Rickettsiales, ticks can also transmit pathogenic unicellular Protista, members of Apicomplexa (Welc-Falęciak *et al.* 2010).

The most characteristic morphological character of the representatives of Apicomplexa is the presence of the so-called apical complex in the conical cell pole. This structure is necessary to penetrate the host's cells. The apical complex is composed of polar rings, conoid, rhoptries and micronemes, which are modified secretory vesicles (Morrissette and Sibley 2002). The apicoplast is a small structure of vesicular shape, evolutionarily derived from a plastid. It plays an important biochemical role in the parasite's cell, for example biosyntesis of fatty acids, isoprenoids, iron-sulphur clusters (Lim and McFadden 2010). All these components of the apical complex play crucial roles in the parasitic mode of life of Apicomplexa.

2. TICK-TRANSMITTED APICOMPLEXA

2.1. *Babesia* spp.

Babesiosis is one of the tick-transmitted diseases caused by Apicomplexa. It was discovered in 1888 by the Romanian scientist Victor Babes (Babes 1888). Over 100 species of the genus *Babesia* have been described to date. Their distribution varies between species. They occur on all continents. Members of the genus *Babesia* are transmitted by hard ticks, e.g. *Ixodes ricinus*, *I. trianguliceps*, *Dermacentor reticulatus*, several species of the genus *Rhipicephalus* and many others (Sonenshine 1993). *Babesia* spp., like other Apicomplexa, have a complicated life cycle including an asexual stage, taking place in vertebrates, and a sexual stage which takes place within arthropods (Fig. 1). Because of this, the ticks are ultimate hosts and vertebrates are intermediate hosts. Individual hosts are relatively specific to particular species. For *B. microti* they are *Microtus* spp. and other small mammals, for *B. canis* – *Canis* spp., and for *B. divergens* – cattle and deers such as *Capreolus capreolus* (Duh *et al.* 2005, Cieniuch *et al.* 2009, Vannier and Krause 2009).

Babesiosis is, first of all, an animal disease. It occurs most often in cattle, dogs and forest animals, but in certain conditions also people can get infected. This pertains to such species as *B. divergens* and *B. microti* (Kjemtrup and Conrad 2000, Hünfeld *et al.* 2002, Hildebrandt *et al.* 2007). The two immunocompetent patients, Martinot *et al.* (2011) described, had clinical symptoms. Nevertheless, *Babesia* spp. infections can also be asymptomatic, even in immunosuppressed persons.

There are many factors which distinctly increase the infection risk. They include age, immunological dysfunctions, taking immunosuppressive drugs or sterides and splenectomy (Vannier and Krause 2009). These factors have also a distinct effect on the course of the disease. Since *Babesia* spp. can remain undetected for long periods, a potential route of infection can be blood transfusion from an infected person (Gubernot *et al.* 2009). There are also few reports on the possibility of penetration of parasites to the foetus through the placenta (Pantanowitz *et al.* 2002).

2.1.1. Clinical and diagnostic aspects

The course of the disease depends on many factors, and its syptoms are not easy to identify, hence the proper diagnosis is often time-consuming. Clinical symptoms of babesiosis are not specific (Zygner 2006). They include the malaise, fever, headache, muscular aches and digestive system problems such as nausea, stomach ache, vomiting and diarrhoea. With time, they may be joined by joint aches, loss of weight, jaundice, kidney damage accompanied by dark-coloured urine. Consequences of babesiosis may also include acute respiratory insufficiency, anemia, heart insufficiency, hypertension and failure of cardiac muscle blood supply. Babesiosis is sometimes fatal, especially for patients with spleenectomy or with disturbed immunological response (Vannier and Krause 2009).

The basic methods used for diagnosing babesiosis are mainly based on observation of clinical symptoms, microscopic examination of blood smears stained with the Giemsa method and serological analysis. However,

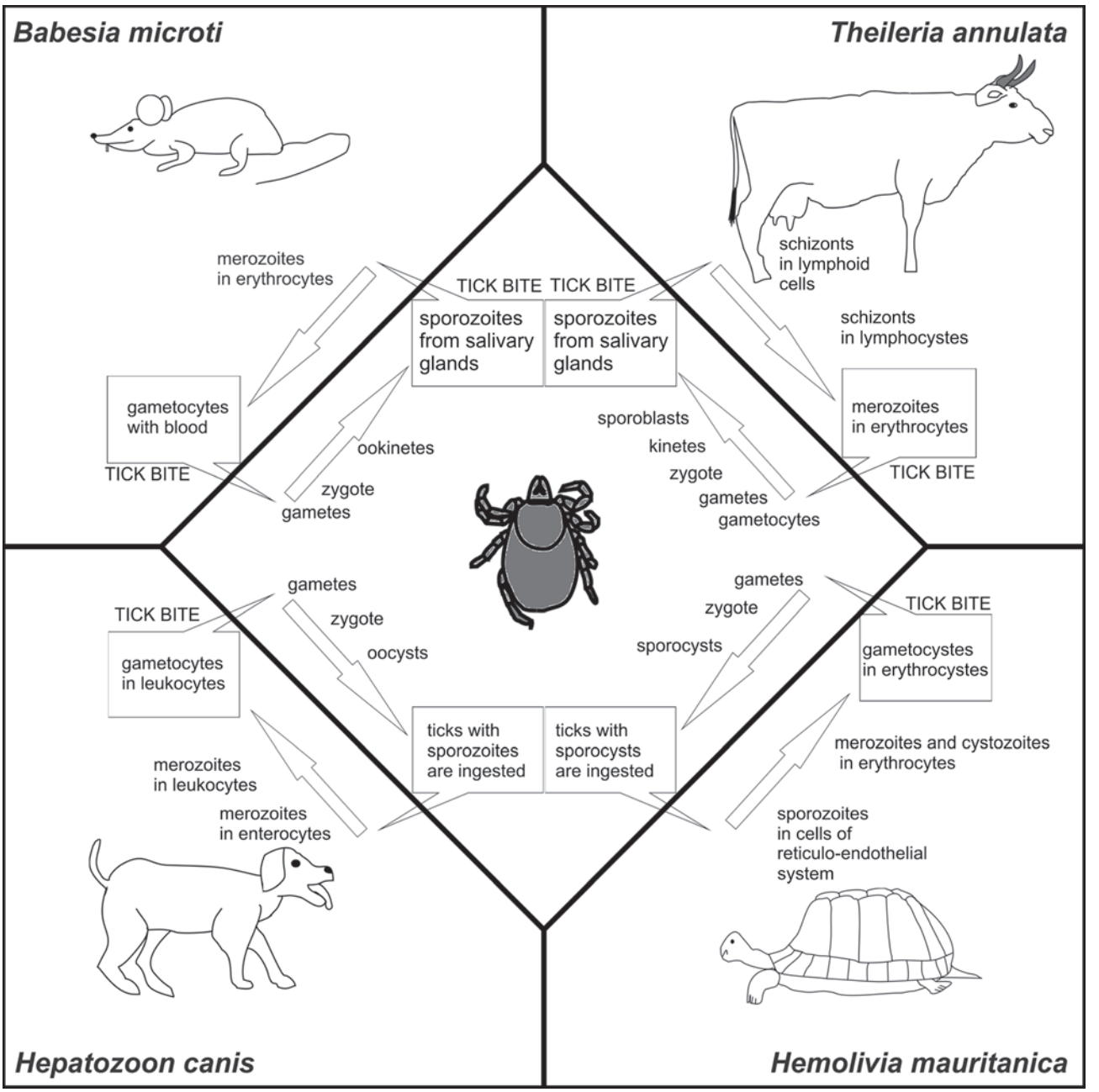

Fig. 1. A schematic drawing of developmental cycles.

finding *Babesia* spp. in erythrocytes of infected people is difficult and may be confused with infection with *Plasmodium* spp., while serological tests show only the existence of antibodies which may result from the chronic form of the disease or earlier contact of the patient with representatives of *Babesia* (Yoshinari *et al.* 2003). It is also difficult to ascertain if the anemia is caused by babesiosis. The diagnostic difficulties made it necessary to seek new methods. Analysis for the presence of DNA of *Babesia* spp. with PCR technique is used increasingly often (Irvin 2009).

The therapy of babesiosis patients is based on administration of four different drugs: clindamycin combined with quinine and atovaquone with azithromycin

(Krause *et al.* 2000, Vannier and Krause 2009). Sometimes in severe cases the therapy has to involve blood transfusion (Fox *et al.* 2006).

2.2. *Theileria* spp.

Species of the genus *Theileria* form a large group which is related to *Babesia* and are also classified within Apicomplexa; Piroplasmida. These parasitic organisms, like *Babesia* spp., are characterised by a complex life cycle (Fig. 1). Their intermediate hosts can be mammals, specific to each parasite species, while ultimate hosts are various hard ticks. The geographical range of *Theileria* spp. varies. Theileriosis is first of all a disease of cattle and small ruminants. It poses a serious veterinary, and consequently economic, problem. The fact that theileriosis is a serious problem in the Third World countries, for example in eastern, southern and central Africa, can not be ignored.

T. parva causes the so-called East Coast Fever (ECF) of cattle. The species spreads through ticks of the genus *Rhipicephalus* and causes considerable economic losses (Katzer *et al.* 2010). Besides *T. parva* in Africa, ethiological factors of cattle theileriosis include *T. annulata*, *T. mutans*, *T. taurotragi* and *T. velifera*. Cases of theileriosis were also recorded in America (*T. cervi*, *T. equi*, *T. sergenti*), Asia (*T. annulata*), as well as western, southern and eastern Europe (*T. annulata*, *T. hirci*, *T. ovis*). The last two of the mentioned parasites attack mainly sheep and are transmitted by ticks of the genera *Hyalomma*, *Rhipicephalus*, *Dermacentor*, *Haemaphysalis* (Mitema *et al.* 1991, Sonenshine 1993, Viseras *et al.* 1997, Criado-Fornelio *et al.* 2003).

2.2.1. Clinical and diagnostic aspects

Various species of the genus *Theileria* show different pathogenicity. The incubation period of theileriosis lasts from a few days to three weeks. The course of the disease can be chronic or acute. The first symptom after the incubation period is a considerable swelling of lymphatic nodes. Besides the typical symptoms there is a loss of appetite, diarrhoea and a deep respiratory insufficinecy as a result of pneumothorax. Besides these universal symptoms of theileriosis, there are symptoms specific to particular species. For example *Theileria parva* causes lymphocytosis, while hemolytic anemia and haemoglobinuria appear in cases of infection with *T. annulata* and *T. mutans*. The specificity of the symptoms is associated with the differences in the life cycles and affinity to various host cells. For example, *T. parva* invades only mammal lymphocytes and *T. mutans* mainly erythrocytes.

Diagnosing theileriosis involves mainly observation of clinical symptoms, analysis of blood smears and smears of lymphatic node biopsies. Serological and molecular methods with the use of PCR technique and nucleic acid sequencing can also be used (Sawczuk 2006, Branco *et al.* 2010).

Prophylaxis and therapy depend mainly on the economic condition of the region. Possibilities of therapy using inhibitors of metabolic processes in the apicoplast are being analysed (Lizundia *et al.* 2009).

2.3. *Hepatozoon* spp.

Hepatozoidae form a rather large family within Apicomplexa; its members are parasites of various vertebrates and invertebrates. Complex life cycles of *Hepatozoon* spp. (Fig. 1) require two or more hosts. Intermediate hosts are vertebrates while invertebrates are ultimate hosts. *H. sipedon* requires three hosts to complete its life cycle. Its intermediate hosts are amphibians and snakes which devour the infected amphibians; the ultimate host is a mosquito of the genus *Culex* (Smith *et al.* 1994). Intermediate hosts for many representatives of the genus *Hepatozoon* are mammals; ultimate hosts are ticks. The best known are species which cause hepatozoonosis in dogs. It is characteristic that the infection gate of intermediate hosts is the digestive system. The dogs become infected as a result of eating ticks whose haemolymph contains oocysts; in the dog's gut they release sporozoits which penetrate the hosts's intestine (Ewing and Panciera 2003). *H. canis* and *H. americanum* are phylogenetically related but differ in their geographical distribution, vector specificity and effect on the hosts. *H. canis* is common in Asia, western, southern and eastern Europe (Paşa *et al.* 2009), in Africa and South America (Rubini *et al.* 2009). Recently the occurrence of *H. canis* has also been reported from North America (Little *et al.* 2009). *H. americanum* occurs in southern, central and south-eastern parts of the USA. The range is correlated with the occurrence of the typical ultimate host of the parasite, the tick *Amblyomma maculatum* (Garret *et al.* 2005). The ultimate host of *H. canis* is mainly *Rhipicephalus sanguineus*, but the role may be also played by other ticks such as *Amblyomma cajennense*, *A. ovale* or *A. aureolatum* (Rubini *et al.* 2009).

2.3.1. Clinical and diagnostic aspects

Canine hepatozoonosis caused by *H. canis* can be asymptomatic. In cases of immunological insufficiency or co-infection and weakening of the dog's organism, fe-

ver, general weakening, loss of appetite and weight loss may appear. Blood smears indicate neutrophilia and the presence of parasites in the neutrophiles (Baneth *et al.* 2003, Baneth and Vincent-Johnson 2005). *H. americanum* causes acute or chronic symptoms. In the first case, besides fever, malaise, loss of appetite and weight, also leucocytosis, swelling of lymphatic nodes, damage to the liver, hypoglycaemia or myositis may occur. Chronic, long-lasting infection may cause histopathological changes within the skeleton and muscles, leading to motoric disorders (Potter and Macintire 2010).

Diagnosing hepatozoonosis in dogs is based on observation of smears of peripheral blood, smears of lymphatic node biopsies, analysis of skeletal muscle biopsies and X-ray analysis of long bones in which periosteum proliferation is a characteristic symptom. Molecular methods, Western blot analysis and PCR, are used in some cases (Ewing and Panciera 2003, Zygner 2006).

The therapy most often involves combined treatment called TCP, which consists in administration of trimetoprim-sulfonamide, clindamycin and pirymethamine (Medici and Heseltine 2008).

2.4. *Hemolivia* spp.

Protists of the genus *Hemolivia* are parasites of poikilothermic vertebrates and arthropods. The processes of gamogony, merogony or cystogony occur in the intermediate hosts's body, which may be an amphibian or a reptile. Fertilisation, oocyst and sporocyst forming take place in the tick, representing the ultimate host (Široký *et al.* 2007).

Among *Hemolivia* spp., which have been known for about 100 years, *Hemolivia mauritanica* was described as a parasite of the turtle *Testudo mauritanica*, which is a typical component of Algerian fauna (Sergent and Sergent 1904). As a result of further studies on the life cycle and the structure of various development stages, the species was classified as a member of the genus *Hepatozoon*. Later taxonomic studies ultimately confirmed the distinctness of the species and placed it in the genus *Hemolivia* (Landau and Paperna 1997). *H. mauritanica* is a parasite of turtles of the genus *Testudo* (Fig. 1), both in the wild and in captivity (Široký *et al.* 2004, Široký *et al.* 2005). The ultimate host of *H. mauritanica* is the tick *Hyalomma aegiptium* (Široký *et al.* 2007).

Hemolivia stellata is a member of Apicomplexa which parasitises amphibians. Its ultimate host is *Amblyomma rotundatum*. Sporocysts formed in the tick gut are transmitted orally (through eating the tick) to the intermediate host which is *Bufo marinus* (Široký *et al.* 2007). Some authors emphasize the importance of cyst formation in the development of *Hemolivia*. This is important because of the oral way of infection of the intermediate host (Petit *et al.* 1990).

The natural intermediate host of *Hemolivia mariae* is *Tiliqua rugosa*, and the ultimate host is *Amblyomma limbatum* (Smallridge and Bull 1999). Species specificity of intermediate and ultimate hosts of *H. mariae* is not completely obligatory. Experimental studies involving infecting atypical intermediate hosts such as *Mabuya vitatta* and *Agama stellio* showed that the parasite's development could be physiologically adapted to the atypical intermediate host. Such adjustment is associated with structural changes of merozoites and early stages of intraerythrocytic gametocytes (Paperna and Smallridge 2001).

2.4.1. Clinical and diagnostic aspects

Because the processes of merogony, cystogony and gamogony take place in the intermediate hosts, gametocytes, merozoites or cystozoites can be observed in blood smears. Initial phase of merogony occurs in intestine, liver and kidney cells.

Parasitaemia often has a mild course. Only in the case of mass or prolonged invasion nephrotic syndrome and liver degeneration may develop (Široký *et al.* 2007).

Apicomplexa are a large and diverse group of Protista, including more than 5000 species. All representatives of this group show specific life cycle. Beside morphological and physiological variety, individual species also present different host invasion strategies.

Most of the publications describing those of Apicomplexa species important to humans, concern ethiological agents of malaria and toxoplasmosis. In this work we want to highlight the importance of some Apicomplexa species, which are transmitted by ticks. Although these are mainly animal parasites, they may be of some importance as humans may become accidental hosts or bear significant economic loss due to disease of livestock animals.

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