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ScienceDirect
International Journal for Parasitology 38 (2008) 1219–1237
www.elsevier.com/locate/ijpara

Babesiosis: Recent insights into an ancient disease

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Received 3 January 2008; received in revised form 29 February 2008; accepted 3 March 2008

Abstract

Ever since the discovery of parasitic inclusions in erythrocytes of cattle in Romania by Victor Babes at the end of the 19th century, newly recognised babesial pathogens continue to emerge around the world and the substantial public health impact of babesiosis on livestock and man is ongoing. Babesia are transmitted by ixodid ticks and infection of the host causes a host-mediated pathology and erythrocyte lysis, resulting in anemia, hyperbilirubinuria, hemoglobinuria, and possibly organ failure. Recently obtained molecular data, particularly for the 18S rRNA gene, has contributed significantly to a better understanding of the sometimes puzzling phylogenetic situation of the genus *Babesia* and new information has been added to help determine the taxonomic position of many species. Moreover, it seems that owing to higher medical awareness the number of reported cases in humans is rising steadily. Hitherto unknown zoonotic babesias are now being reported from geographical areas where babesiosis was not known to occur and the growing numbers of immunocompromised individuals suggest that the frequency of cases will continue to rise. This review covers recent insights into human babesiosis with regard to phylogeny, diagnostics and treatment in order to provide new information on well known as well as recently discovered parasites with zoonotic potential.

Keywords: *Babesia*; Ticks; Zoonosis; Phylogeny; Human disease; Blood transfusion; IFAT; PCR; Diagnostics; Treatment; Prevention

1. Introduction

Tick-transmitted hemoparasites of the protozoan genus *Babesia* (phylum Apicomplexa) are the second most common blood-borne parasites of mammals after the trypanosomes (Telford et al., 1993). It was Victor Babes who at the end of the 19th century first discovered microorganisms in erythrocytes of cattle in Romania and associated them with bovine hemoglobinuria or red water fever (Babes, 1888). Five years later, Smith and Kilbourne established *Pyrosoma* – later renamed *Babesia bigemina* – as the causative agent of Texas Cattle Fever (Smith and Kilbourne, 1893), a finding of historic significance because this piroplasm was the first recognised arthropod-borne pathogen of vertebrates (Kjemtrup and Conrad, 2000). Since then, newly recognised babesia with zoonotic potential continue to emerge around the world and the substantial economic impact of babesiosis on livestock and companion animals especially in the tropics and subtropics is ongoing (Collett, 2000; Kivaria et al., 2007). A fatal *Babesia divergens* infection in 1956 was the first confirmed case of human babesiosis (Skrabalo and Deanovic, 1957) and, ever since, babesiosis came into view as a potentially life threatening zoonotic infection in humans (Homer et al., 2000; Herwaldt et al., 2003). Although, several babesia species have been involved in human infections worldwide (Gorenflot et al., 1998), the major public health burden on man lies in North America and is due to *Babesia microti*, especially in the eastern parts of the US (Homer et al., 2000). In these classic areas of endemicity, babesiosis is on the rise and the number of cases appears to be increasing in some parts of the US relative to the number of Lyme

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doi:10.1016/j.ijpara.2008.03.001

disease cases (Meldrum et al., 1992; Krause et al., 2003). Moreover, during the last decade, newly recognised babesia parasites (Table 1) have been implicated in human disease and it seems that owing to higher medical awareness the number of reported cases is rising steadily (Hildebrandt et al., 2007). In addition, the occurrence of hitherto unknown zoonotic parasites is now reported from geographical areas where babesiosis was not known to occur and obviously the growing population of immunocompromised individuals is ever more involved (Hunfeld and Brade, 2004; Häselbarth et al., 2007; Hildebrandt et al., 2007; Karp and Auwaerter, 2007). Most significantly, molecular analysis of the implicated pathogens suggests that the host-range of many babesia is less restricted than believed previously and also that hitherto unrecognised species can cause infections in a variety of animal hosts and in humans (Zahler et al., 2000; Cho et al., 2002; Herwaldt et al., 2003, 2004; Conrad et al., 2006; Kjemtrup et al., 2006; Häselbarth et al., 2007; Kim et al., 2007). Therefore, many past cases of human babesiosis on both sides of the Atlantic that were attributed, based on traditional methods, to classic species such as *B. divergens* or *B. microti*, may indeed be due to species not yet known to cause such infections in humans (Herwaldt et al., 2003; Gray, 2006; Hildebrandt et al., in press). This notion is further substantiated by the recent recognition of *Babesia duncani* and *B. divergens*-like organisms as pathogens of medical significance for humans in the US (Herwaldt et al., 1996; Beattie et al., 2002; Conrad et al., 2006). Moreover, confirmed autochthonous *B. microti* infections have been reported in Taiwan, Japan and Europe (Shih et al., 1997; Saito-Ito et al., 2000; Hildebrandt et al., 2007), and a new European *B. divergens*-like organism (EU1), provisionally named *Babesia venatorum*, has been discovered, which is probably a parasite of deer (Telford and Goethert, 2004; Bonnet et al., 2007). This parasite was involved in the first documented cases of human babesiosis in Italy, Austria and Germany (Herwaldt et al., 2003; Häselbarth et al., 2007). Such new findings now clearly challenge the dogma that human babesiosis in North America is almost exclusively caused by *B. microti* and that human babesiosis in Europe is solely due to *B. divergens* infection in splenectomized individuals. This review covers recent developments and important new information on well known and recently discovered babesias with zoonotic potential.

2. Classification and life cycle characteristics of *Babesia* spp.

Babesia are classified as apicomplexan parasites of the suborder Piroplasmidea and family Babesiidae on the basis of their exclusive invasion of erythrocytes, multiplication by budding rather than schizogony, and lack of hemozoin. The life cycles of the parasites are very similar (Fig. 1). All species of babesia are naturally transmitted by the bite of infected ticks (almost all ixodids rather than argasids) and the main lifecycle difference amounts to the presence of transovarial transmission in some species (*Babesia* spp. sensu stricto) and not in others (*B. microti*-like). During the tick bite, sporozoites are injected into the host and directly infect red blood cells (Fig. 1). This phenomenon separates *Babesia* spp. from *Theileria* spp., where sporozoites do not readily infect red blood cells but initially penetrate a lymphocyte or macrophage in which development into schizonts takes place (Uilenberg, 2006). In the host, babesia sporozoites develop into piroplasms inside the infected erythrocyte resulting in two or sometimes four daughter cells that leave the host cell to infect other erythrocytes until the host dies or the immunity of the host clears the parasites. The spleen with its lympho-reticular filter function is essential in resisting primary infections of *Babesia* spp. by specifically removing infected cells from circulation, probably through a combination of spleen microcirculation and stimulated phagocytic cell activity (de Vos et al., 1987; Gray and Weiss, 2008).

To date, more than 100 species have been identified, infecting many mammalian and some avian species (Gray and Weiss, 2008). Traditionally, babesias were mainly grouped on the basis of their morphology, host/vector specificity, and susceptibility to drugs. Pragmatically, they are divided into the small babesias (trophozoites of 1.0–2.5 μm; including *Babesia gibsoni*, *B. microti*, and *Babesia rodhaini* and large babesias (2.5–5.0 μm; including *Babesia bovis*, *Babesia caballi*, and *Babesia canis*). These morphological classifications are generally consistent with the phylogenetic characterization based on nuclear small subunit-ribosomal RNA gene (18S rDNA) sequences, which shows that the large and small babesias fall into two phylogenetic clusters, with the small babesias being more related to *Theileria* spp. than the large (with the exception of *B. divergens*, which appears small on blood smears [0.4–1.5 μm] but is genetically related to large babesias (Homer et al., 2000). Recently, molecular genetic analyses clarified the somewhat confused phylogenetic situation, sometimes resulting in the emergence of new groups and 18S rDNA analysis added new information to the taxonomic position of many piroplasm species (Kjemtrup and Conrad, 2006). A careful study by Criado-Fornelio et al. (2003) recently suggested division of the piroplasms into five distinct clades: (i) *B. microti* group containing *B. rodhaini*, *Babesia felis*, *Babesia leo*, *B. microti*, and a *B. microti*-like canine isolate, (ii) western US *Theileria*-like group, containing *Babesia conradae*, (iii) *Theileria*-group, containing all *Theileria* species from bovines, (iv) a first group of 'true' *Babesia* spp. (sensu stricto) including *B. canis* and *B. gibsoni* from canines together with *B. divergens* and *Babesia odocoilei*, and (v) a second *Babesia* spp. sensu stricto group composed mainly of *Babesia* spp. from ungulates: *B. caballi*, *B. bigemina*, *B. ovis*, *B. bovis*, and other *Babesia* spp. from cattle.

2.1. New developments in the phylogeny of *B. microti* and *B. microti*-like organisms

Latest research suggests that *B. microti* is only distantly related to *Babesia* species sensu stricto (*B. bigemina*, *B. bovis*, and *B. divergens*), that are best known as parasites