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MINI-REVIEW

Identity of the causal agents of human babesiosis in Europe

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Abstract

Most cases of human babesiosis are caused either by *Babesia divergens* in Europe or *Babesia microti* in America. *B. microti*, once regarded as a single species, occurs as a world-wide species complex and although both phenotypic and genotypic features lend support to suggestions that zoonotic *B. microti* may occur in Europe, convincing medical evidence is lacking. Several *B. divergens*-like parasites have emerged in the last few years, but 18S rRNA gene analysis suggests that *B. divergens* 'sensu stricto' is restricted to European (and North African) cattle. Some of the *B. divergens*-like parasites only differ from the bovine type by a few bases, and it remains to be determined whether this is sufficient to accord them separate species status. Comparative biology should support genetic data in taxonomic studies of both *B. divergens* and *B. microti*.

Keywords: *Babesia divergens*; *Babesia microti*; 18s rRNA gene analysis

Biology and pathology

Babesiosis is caused by tick-transmitted intraerythrocytic protozoan parasites of the genus *Babesia*. These parasites are best known as the cause of animal diseases, particularly of cattle in the tropics and subtropics, but they can also be zoonotic. *Babesia divergens* is the most frequent cause of bovine babesiosis in northern Europe (Zintl et al., 2003) and was probably responsible for the first recorded case of human babesiosis (in Yugoslavia), though the parasite involved was referred to as *Babesia bovis* (Skrabalo and Deanovic, 1957). Interestingly, there is evidence that *Ixodes ricinus* also transmits a *B. bovis*-like parasite (Brossard and Aeschlimann, 1975; Hofmann-Lehmann et al., 2004), but so far no attempts have been made to determine the true identity of this parasite.

B. divergens is widespread in European cattle and probably occurs wherever the vector *I. ricinus* is present, including North Africa (Bouattour and Darghouth, 1996), but the precise humidity requirements of the vector restrict the pathogen to areas with a moisture-saturated micro-habitat at the base of permanent herbage. Countries with the highest incidence of the bovine disease are therefore those where significant tick populations occur in rough open hill-land or damp low-lying meadows, for example Ireland (Gray and Harte, 1985), and where woodland frequently abuts cattle pasture, for example France (L'Hostis and Chauvin, 1999). Since most of the continental-European habitat for *I. ricinus* is woodland and cattle make limited use of such habitat, the distribution of *B. divergens*-infected ticks shows incomplete overlap with the overall distribution of the vector.

Many cases of bovine babesiosis are relatively mild, but case fatality rates may be as high as 10% despite treatment (Gray and Harte, 1985). Severe cases present with high fever, anaemia, anorexia, depression, weakness, cessation of rumination, and an increase in respiratory and heart rate. Parasitaemias may rise to between 30% and 45% causing extensive erythrocyte

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destruction. The resulting haemoglobinuria, which gives the disease the colloquial name of redwater fever, is frequently the first clinical sign detected. In humans, cases present as medical emergencies showing most of the symptoms of the acute bovine disease, including haemoglobinuria. About 31 cases, most incriminating *B. divergens* as the causal agent, have been reported and all have occurred in splenectomized individuals, frequently with further immunocompromising conditions, and characterized by rapid fulmination (Zintl et al., 2003). The Mongolian gerbil (*Meriones unguiculatus*), a laboratory host, is highly susceptible to bovine isolates of *B. divergens* (Gray and Parr, 1992; L'Hostis and Chauvin, 1999), a feature that can be exploited for the identification of babesias involved in human infections.

The other main cause of human babesiosis is *Babesia microti*, a rodent parasite, the vast majority of human cases occurring on the north-eastern seaboard of the USA (Kjemtrup and Conrad, 2000). In contrast to *B. divergens*, *B. microti* can give rise to disease in spleen-intact patients, manifesting as malaise, myalgia, anorexia, and mild fever. Acute cases can occur but most infections are probably subclinical and persistent. *B. microti* is also widespread in Europe, but so far there is no firm evidence that European *B. microti* can cause human disease. Data presented in a recent publication (Meer-Scherrer et al., 2004) that claimed to report the first autochthonously acquired case in Europe are unconvincing. Although the clinical presentation was persuasive, immunofluorescence assay titres were very low, intraerythrocytic inclusions identified in photographs as parasites appear to be platelets, and the PCR was negative at a time when parasites were reportedly observed in blood smears. Some positive PCR results were obtained, but unfortunately the product was not sequenced.

It is probable, however, that *B. microti* human infections, if not clinical cases, do occur in Europe. At least one strain has been shown to be transmitted by *I. ricinus* (Walter, 1984; Gray et al., 2002), and *B. microti* has been detected in *I. ricinus* specimens collected from vegetation (Duh et al., 2001; Skotarczak and Cichocka, 2001; Foppa et al., 2002; Kalman et al., 2003). Serological evidence for human infection with *B. microti* also exists (Krampitz et al., 1986; Hunfeld et al., 2002; Foppa et al., 2002) but no isolations of parasites have been made from human patients despite speculation that *B. microti* infection may underlie atypical presentations of Lyme borreliosis. The zoonotic status of *B. microti* in Europe must therefore remain open to question. Future attempts to identify human cases of *B. microti* infection in Europe should include blood transfer to susceptible laboratory hosts, such as hamsters or gerbils, and also the sequencing of any PCR products obtained.

Parasite identity

The identity of *Babesia* isolates has traditionally been determined by morphology and serology. Morphology is not useful for closely related parasites, especially since the appearance of a particular species may vary in different hosts (Gray et al., 2002). The main serological method in use for *Babesia* spp. is indirect immunofluorescence, but this approach is also unreliable for closely related parasites. For example, bovine *B. divergens* isolates cannot be differentiated from similar parasites isolated from deer (Gray et al., 1990; Langton et al., 2003), although antigenic diversity has been reported in this species (Phillips et al., 1987). Antigenic variation in *B. microti* has also been detected, using immunoblot methods (Homer et al., 2000). Immunoblots provide opportunities for greater analysis of antigenic differences in *Babesia* spp. (Homer et al., 2000; Ryan et al., 2001) and have been used to differentiate cattle blood parasites in Europe (Edelhofer et al., 2004), but have not so far been used in intraspecific taxonomic studies. In contrast, several research groups have used molecular tools for taxonomic purposes, including studies on the identity and interrelatedness of the parasites involved in human babesiosis. This review focuses on the topic from a European perspective, specifically addressing the questions of what parasites are involved in acute human babesiosis, and how variable and potentially zoonotic European strains of *B. microti* may be.

Babesia divergens

In recent years several parasites have been identified as *B. divergens* following genotypic analysis, despite them showing features that are not typical of the classic bovine type. For example, an isolate from an unusual host, the reindeer, *Rangifer tarandus*, in Scotland, was described as *B. divergens* on the basis of 99.8% homology of the 18S rRNA gene with a GenBank type isolate, although the parasite was not infective for gerbils and no bovine babesiosis cases occur in the local area (Langton et al., 2003). Similarly, *B. divergens* was identified as the causal agent in red and roe deer in Slovenia (Duh et al., 2005) and in human cases in unusual geographical areas, such as the Canary Islands (Olmeda et al., 1997), Kentucky, USA (Beattie et al., 2002), and southern Portugal (Centeno-Lima et al., 2003). One North American (Nantucket) isolate that was designated *B. divergens* also occurred in an unusual host, the eastern cottontail rabbit (*Sylvilagus floridanus*) (Goethert and Telford, 2003). Other isolates from humans have been described as *B. divergens*-like (Herwaldt et al., 1996, 2004) or *B. odocoilei*-like (Herwaldt et al., 2003).