Parasites & Vectors

REVIEW Open Access

Why is Southern African canine babesiosis so virulent? An evolutionary perspective

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Abstract

Canine babesiosis is a common, highly virulent disease in Southern Africa with even pups and juveniles being severely affected. This contrasts with bovine babesiosis, for example, where host, parasite and vector co-evolved and young animals develop immunity after infection without showing clinical signs. *Babesia rossi*, the main causative organism of canine babesiosis in sub-Saharan Africa, was first described from a side-striped jackal (*Canis adustus*) in Kenya. Although data are meagre, there is evidence that indigenous African canids, such as jackals and wild dogs (*Lycaon pictus*), can harbour the parasite without showing untoward effects. Dogs are not indigenous to Africa. The vast majority of dogs presented at veterinary facilities in South Africa represent recently introduced European, Asian or American breeds. The contention is that *B. rossi* is a new challenge to which these dogs have not adapted. With intensive treatment of clinical cases, natural selection is effectively negated and the status quo will probably be maintained indefinitely. It is postulated that *Babesia vogeli*, which frequently results in unapparent infections or mild manifestations in dogs, represents or is closely related to the ancestral form of the canine parasite, possibly originating from wolves (*Canis lupus*).

Introduction

Babesiosis is one of the most important canine diseases in South Africa. Countrywide, babesiosis is diagnosed in around 10% of dogs presented to veterinary practices [1]. At the Onderstepoort Veterinary Academic Hospital on the outskirts of Pretoria, South Africa, around 12% of sick dogs presented are diagnosed with babesiosis, and around 31% of these are admitted for more intensive treatment [2]. Canine babesiosis, referred to as "malignant jaundice or bilious fever", was first reported from the Cape Colony in 1893 [3]. Early reports alluded to the virulent nature of the disease in South Africa [4-6], which differed from the manifestation in other parts of the world. Working with a South African isolate, Nutall and Hadwen (1909) commented that the parasites used in experiments in Italy must have been much less virulent than theirs [7,8]. Furthermore, dogs that survived infection with a French isolate were fully susceptible to the South African one, prompting Laveran & Nattan-Larrier to conclude in 1913 that the African babesia of dogs, if not a separate species, was at least a variety distinct from the French one [9,10].

It was soon evident that isolates from different geographic regions were vector-specific. South African isolates were transmitted by *Haemaphysalis elliptica*, previously misidentified as *Haemaphysalis leachi* [4,11]. Isolates from North Africa, the Middle East and India were transmitted by *Rhipicephalus sanguineus*, while those from Southern Europe were transmitted by *Dermacentor reticulatus* [12-14]. Later research confirmed this vector-specificity [15,16].

It is rather curious, therefore, that generally no notice was taken of this clear evidence of distinct biological differences between region-specific isolates. Until 20-odd years ago, it was generally accepted that babesiosis in dogs was caused by two species: a large piroplasm, *Babesia canis*, and a small one, *Babesia gibsoni*. Although the parasites had some characteristics in common, the disease manifestations were distinct. In 1989, Uilenberg *et al.* [17] reminded the scientific community that three distinct taxa were generally lumped under the "large" *Babesia*: *B. canis* (*sensu stricto*) [18], transmitted by *Dermacentor reticulatus*, occurring in Southern Europe, but seemingly spreading northwards [19,20]; the cosmopolitan *B. vogeli* [21], transmitted by *Rhipicephalus sanguineus*; and *B. rossi* [22],

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transmitted by *Haemaphysalis elliptica*, restricted to sub-Saharan Africa. It was subsequently demonstrated that these three taxa can de differentiated molecularly as well [23]. A fourth, as yet unnamed, large *Babesia* has since been reported from dogs in the USA [24].

Pre-1990 literature on canine babesiosis should therefore be considered cautiously, as the actual causative agent may be in doubt. Although *B. vogeli* has been recorded in South Africa, it seems to be relatively rare and the large body of literature on canine babesiosis, especially concerning pathogenesis and clinical manifestation, can be safely attributed to *B. rossi* [25,26]. Similarly, most references from Europe probably refer to *B. canis* (*sensu stricto*). Elsewhere, *B. vogeli* would probably be the causative agent. Persisting in merely referring to "canine babesiosis" without specifying the causative agent, is scientifically unsound.

The "small" piroplasm does not refer to a single species either. At least five taxa have been described: *Babesia gibsoni* (*sensu stricto*) [27], *Babesia conradae* [28], a *Babesia microti*-like organism [29], *Theileria annae* [30] and an unnamed *Theileria* species [31].

Clinical manifestation of *B. rossi* infection

The earliest scientific descriptions of canine babesiosis in South Africa are of a highly virulent disease [4-6]. Subsequent intensive study has borne this out.

Babesia rossi causes peracute and acute disease, the clinical signs including pale mucous membranes, depression, tachycardia, tachypnoea, anorexia, weakness, splenomegaly and fever [32]. The clinical signs are attributed to tissue hypoxia resulting from anaemia and a concomitant systemic inflammatory response syndrome caused by marked cytokine release [33]. The severe form of the disease is characterised by haemolytic anaemia and severe acid-base derangements [34], with secondary multiple organ failure and complications such as acute renal failure, hepatopathy with marked icterus, hypoglycaemia [35], acute respiratory distress syndrome, cerebral pathology and additional immune-mediated erythrocyte destruction [32,36]. Mortality is around 12% [32]. A feature of the disease is that, in contrast to babesiosis in other domestic species, pups and immature dogs are also badly affected [32,37].

In contrast, *B. vogeli* infection in mature dogs is often unapparent or results in moderate clinical signs only, with the parasitaemia appearing to be low [32]. Although subclinical infections are common in adult dogs, pups tend to present with marked anaemia [38]. *Babesia canis* infection results in a more varied pathogenicity, intermediate between the other two species [32].

The question arises, therefore: why is *B. rossi* more virulent than the other two taxa? It is contended that, from an evolutionary perspective, domestic dogs have not had sufficient time to adapt to this parasite. Let us consider some examples where parasite and host apparently evolved together.

Endemic stability in bovine babesiosis

Babesia bovis and *Babesia bigemina* are major causative agents of bovine babesiosis, especially in tropical and subtropical regions, where they are thought to have evolved [39]. Although some other hosts can be infected, usually artificially, both species are primary parasites of cattle [39]. Similarly, the vectors involved, at least in the Old World, are the bovine-specific *Rhipicephalus* (*Boophilus*) *microplus* and *Rhipicephalus* (*Boophilus*) *decoloratus* [40]. It can be concluded, therefore, that co-evolution occurred between host, vector and parasite. This is further borne out by the fact that all domestic cattle have an inherent capacity to cope with infection and to develop immunity to disease without showing clinical signs [41]. This capacity is age-specific, however, and has generally disappeared by the time a calf is one year of age. Under natural conditions, i.e. where no vector control is practised, the parasites would circulate freely in the cattle population. For the first few months of life, calves would be passively protected by maternal antibody ingested with colostrum. Once this protection has waned, calves becoming naturally infected will develop immunity without showing overt clinical signs. The net result is a high prevalence of infection, but a low occurrence of clinical disease. This situation is referred to as endemic stability. This feature is utilised to the advantage of livestock owners: calves vaccinated between 3 and 9 months of age usually develop solid immunity, without showing overt clinical signs [42].

Babesiosis in wildlife

Although not as well studied as in cattle, there is mounting evidence that a similar situation exists in various wildlife species. For instance, black rhinoceroses (*Diceros bicornis*) have been found to harbour *Babesia bicornis* without showing any clinical signs of infection [43]. If black rhinoceroses are stressed, however, either through human intervention such as capture or under natural conditions such as drought, clinical babesiosis may ensue [43-45]. This is attributed to immunosuppression due to stress.

Similarly, a free-ranging sable antelope (*Hippotragus niger*) that had been captured in the low-lying, warm, bushveld region of north-eastern South Africa and transferred to the Johannesburg Zoo, at an altitude of 1800 m, in mid-winter succumbed to babesiosis within a few weeks [46]. It can be assumed that this individual had been a subclinical carrier of the infection. Subsequently,

sable antelopes raised in captivity in Europe and therefore never exposed to infection, were translocated to a game ranch in South Africa, where they contracted babesiosis when housed in an enclosure adjoining one in which wild-caught local sable antelopes were held [47].

A further example is *Babesia leo*, which is prevalent in free-ranging lion populations [48,49]. The death of the famous lioness "Elsa" due to babesiosis after being released in the wild was probably stress-induced [50]. This lioness had repeatedly been severely mauled by the resident lion population [51].

This seems to suggest that a state of equilibrium, i.e. endemic stability, exists, at least in the three examples given. Individuals are able to cope with infection without developing overt clinical signs. This may be dependent on exposure at a young age, as suggested by the captive-bred sable antelopes being fully susceptible to infection, although stress caused by translocation may also have played a role.

How does this pertain to *Babesia* infections in canids?

Babesia rossi infection in African canids

Babesia rossi was first described from a side-striped jackal (*Canis adustus*) in Kenya, and was subsequently also found in blood and organ smears from a jackal pup [22,52]. The literature on babesiosis in indigenous African canids is meagre. The first attempt to infect two black-backed jackals (*Canis mesomelas*) was deemed unsuccessful, as the animals remained clinically normal and subinoculation of their blood to susceptible dogs yielded no results [53]. Subsequently, black-backed jackals artificially infected by subinoculation of blood from infected domestic dogs developed parasitaemia but no overt clinical signs [54,55]. Although fatal clinical babesiosis was reported in an African wild dog (*Lycaon pictus*) pup in the Johannesburg Zoo [56], experimental subinoculation of blood from infected domestic dogs did not precipitate clinical signs in wild dogs [55]. In a large breeding centre, 17/227 (7.0%) of wild dog blood specimens were positive for *B. rossi* [57]. Clinical babesiosis had never been observed in this population, and the infected wild dogs seemed to harbour *B. rossi* with no untoward effect. Trophozoites presumed to be *Babesia canis* (probably *B. rossi*) were seen in 2/29 (6.9%) of wild dog blood smears from the Kruger National Park, South Africa [58], while a single piroplasm, possibly a *Babesia* sp., was seen on a blood smear from 1/16 wild dogs in Serengeti ecosystem, Tanzania [59]. This scant evidence fits the general picture, however, and would seem to suggest that indigenous African canids are able to cope with *B. rossi* infection and become subclinical carriers of the parasite.

Haemaphysalis elliptica, the only known vector of *B. rossi*, is common on South Africa domestic dogs, especially those in peri-urban or rural areas. It is rarely recovered from indigenous canids, but has been reported from captive and free-ranging wild dogs [58,60]. It is much more commonly found on indigenous felids [61-64]. It may be significant that the largest number of *H. elliptica* recovered from an indigenous canid was from a side-striped jackal, the host from which *B. rossi* was originally described [61]. Clinical babesiosis is diagnosed in around 12% of dogs presented at the Onderstepoort Veterinary Academic Hospital, where *H. elliptica* is the most common tick on dogs, while babesiosis was uncommon at another veterinary clinic, situated in a densely populated urban area around 20 km away, where *R. sanguineus* was the most common dog tick recovered [62,65].

In a recent paper on pathogens of domestic and wild canids in Brazil, antibodies to *Babesia* (no species mentioned) were found in domestic dogs only, and not in a small sample of maned wolves (*Chrysocyon brachyurus*), crab-eating foxes (*Cerdocyon thous*) and hoary foxes (*Lycalopex vetulus*) [66]. This may suggest that South American canids are not susceptible to the various *Babesia* species associated with domestic dogs.

Dogs not indigenous to Africa

With the exception of domestic cats (descended from wild cats (*Felis silvestris*), which range throughout Africa and Eurasia) [67] and donkeys [descended from African wild asses (*Equus asinus*)] [68], all domestic animals are exotic to Africa. Domestic dogs have descended from wolves (*Canis lupus*), whose natural distribution is the Palearctic and Nearctic regions [69]. Recent mtDNA data suggest that dogs were domesticated south of the Yangtze River in China, from numerous wolves, less than 16,300 years ago [70].

There is ample evidence that natural selection is facilitating the ability of domestic animals to cope with various sub-Saharan vector-borne pathogens, provided that sufficient time has elapsed since their introduction to the continent. Although not fully resistant, West African Ndama cattle and certain goat and sheep breeds are regarded as tolerant to *Trypanosoma* infections transmitted by tsetse flies (*Glossina* species) [71]. Local breeds of *Bos indicus* (Zebu) cattle, e.g. Nguni and Sanga, exhibit a measure of inherited resistance to heartwater (*Ehrlichia ruminantium* infection, transmitted by *Amblyomma* ticks), probably acquired through millennia of natural selection [72]. This resistance does not prevent infection becoming established, but reduces the severity of clinical disease [72]. *Theileria parva*, primarily transmitted by *Rhipicephalus appendiculatus*, is a natural parasite of African buffaloes which is so virulent to cattle that the host usually succumbs before the

parasite can complete its life cycle. This is the manifestation usually encountered in South Africa, where clinical manifestation is called Corridor Disease [73]. In East Africa, where natural selection has resulted in a certain degree of tolerance developing in cattle, the parasite can complete its life cycle in the host and cattle-to-cattle transmission is the norm. This manifestation is called East Coast fever [74].

Although not indigenous to Africa, genetic characterisation of the Africanis breed, which is endemic in rural areas in South Africa, supports archaeological evidence that dogs were introduced from the Middle East thousands of years ago [75]. A crucial part of the puzzle, which is still lacking, is whether natural selection in Africanis dogs has rendered them resistant or at least tolerant of *B. rossi*.

Most dogs presented to veterinary facilities in South Africa are breeds originating in Europe, Asia and the Americas [37]. As such, they are confronted by an alien parasite, *B. rossi*, and are fully susceptible.

Conclusion

As *B. vogeli* is the least virulent of the species, I contend that it has had the longest association with domestic dogs. It is tempting to speculate that *B. vogeli*, or a closely related form, occurs in wolves, the ancestors of domestic dogs. Unfortunately, information on haemoparasites of wolves appears to be lacking. A further interesting phenomenon is that *Rhipicephalus sanguineus*, the vector of *B. vogeli*, feeds primarily on domestic dogs [76]. *R. sanguineus* has been recorded from captive wolves [77], but seemingly not from free-ranging wolves, although the literature is scanty. Could this imply that *R. sanguineus* has evolved as a dog-specific species during the thousands of years since the domestication of the dog?

It is difficult to speculate where *B. canis* fits into the picture. The widely spread golden jackal (*Canis aureus*) does occur in south-eastern Europe and could possibly be a contender for original host, but this is pure conjecture, as data on haemoparasites and ticks associated with this host are lacking.

It can be confidently stated, though, that *B. rossi* is a natural parasite of indigenous African canids. The vast majority of affected domestic dogs are fairly recent introductions to South Africa that have not yet evolved mechanisms to cope with this infection. As clinically affected dogs are usually treated and generally recover, natural selection is effectively negated and the status quo will probably be maintained indefinitely.

Acknowledgements
Publication of the CVBD6 thematic series has been sponsored by Bayer Animal Health GmbH.

Declaration of competing interests
The author declares that they have no competing interests.

Received: 14 January 2011 Accepted: 13 April 2011
Published: 13 April 2011

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doi:10.1186/1756-3305-4-51
Cite this article as: Penzhorn: Why is Southern African canine babesiosis so virulent? An evolutionary perspective. *Parasites & Vectors* 2011 **4**:51.