Anaplasma phagocytophilum: An emerging but unrecognized tick-borne pathogen

S. EL HAMANI KHATAT1, H. SAHIBI1

(Reçu le 28/01/2015; Accepté le 07/03/2015)

Abstract

Several vector-borne pathogens are considered to be emerging or re-emerging. Among these agents, Anaplasma phagocytophilum is a tick-borne rickettsial bacterium of worldwide distribution. This bacterium is increasingly detected in several parts of the world in both ticks and hosts, including animals and humans. A. phagocytophilum is the causal agent of a zoonotic disease called ‘granulocytic anaplasmosis’ and described in several domestic animals and humans. Currently, human granulocytic anaplasmosis is considered to be the third most important vector-borne disease in both the USA and Europe and is also increasingly diagnosed in some Asian countries. However, in many parts of the world, this disease is unknown and no data are available on its epidemiology.

Key words: Anaplasma phagocytophilum, Granulocytic anaplasmosis, Epidemiology, Vector-borne disease, Zoonosis.

INTRODUCTION

Anaplasma phagocytophilum is an obligate intracellular gram-negative tick-borne rickettsial bacterium of worldwide distribution (Diniz and Breitschwerdt, 2012; Dumler et al., 2005; Woldehiwet, 2010). The bacterium is usually transmitted through the bites of ticks of Ixodes genera (Stuen et al., 2013; Swanson et al., 2006). This organism develops within intracytoplasmic inclusions in granulocytic cells mainly neutrophils (Diniz and Breitschwerdt, 2012; Dumler et al., 2005; Woldehiwet, 2010). A. phagocytophilum infects a wide variety of wild and domestic animals and causes an emerging zoonotic tick-borne disease called granulocytic anaplasmosis (Beugnet and Marié, 2009; Dumler et al., 2005; Keesing et al., 2014).

Tick-borne pathogens, a rising hazard in veterinary and human medicine

Vector-borne diseases (VBDs) are caused by various infectious agents including parasites, bacteria and viruses that are transmitted to a host through the bites of hematophagous arthropods (Baneth, 2014; Beugnet and Marié, 2009; Heyman et al., 2010). A wide variety of VBDs affect both human and animals (Heyman et al., 2010). Ticks are considered to transmit the widest number of pathogens when compared to other arthropod vectors. Several of these pathogens are of veterinary and medical importance and cause various diseases including anaplasmosis, babesiosis, Lyme borreliosis, ehrlichiosis and rickettsiosis (Baneth, 2014; Heyman et al., 2010; Nijhof et al., 2007). In geographic areas where mosquitoes are not prevalent, TBDs are the primary causes of VBDs (Baneth, 2014; Michelet et al., 2014). VBDs and more specifically tick-borne diseases (TBDs) are a growing economic problem causing serious depression in livestock production worldwide (Heyman et al., 2010). Furthermore, canine VBDs have been of increased focus interest because they constitute an important threat to both canine and human health and are thus of major zoonotic relevance (Krämer et al., 2014; Rizzoli et al., 2014; Schreiber et al., 2014). Human is mostly not considered the main host target of tick-borne pathogens contrary to other vector-borne pathogens such as malaria or leishmaniasis, but an accidental host contaminated during the circulation between the vector and the wildlife host (Baneth, 2014; Michelet et al., 2014).

Several VBDs are considered to be emerging in new regions or re-emerging and changes in their epidemiological features are described including extension of geographical distribution, changes in pathogenicity and increased prevalence (Beugnet and Marié, 2009; Rizzoli et al., 2014; Swanson et al., 2006). Indeed, several TBDs have been
recently reported in previously not affected areas such as babesiosis in northern Germany, Belgium, Poland and the Netherlands, *Candidatus Neoehrichia mikurensis* in central and northern Europe and Africa, canine monocytic ehrlichiosis is reported to extend from southern Europe to northern areas of France and described recently in Poland, Belgium and the Netherlands, tick-borne encephalitis virus is also extending to northern parts of Europe and granulocytic anaplasmosis in northern Europe (Beugnet and Marié, 2009; Day, 2011; Heyman et al., 2010; Krämer et al., 2014; Schreiber et al., 2014).

Multiple factors are supposed to play a crucial role in ticks expansion, mainly increased animal travelling, climatic changes with global warming, landscape changes, rehabilitation and management with increased urbanization, development of large suburban areas with private gardens, creation of artificial lakes, deforestation and reforestation, increased open-air activities, changes in wild fauna, loss of biodiversity and decreased host population densities (Baneth, 2014; Day, 2011; Rymaszewska and Adamska, 2011; Yancey et al., 2014). All these conditions affect the ecology and epidemiology of infectious diseases, enable the circulation, multiplication and spread of both vectors and pathogens into formerly unaffected areas, promote the creation of niches for vectors and the capacity to vector newly acquired pathogens, and also increase the risk for the host to enter in contact with vectors (Baneth, 2014; Day, 2011; Krämer et al., 2014; Yancey et al., 2014).

The combination of urbanization, climate changes and landscape modification in urban and peri-urban areas create favorable conditions to further increase ticks populations, extend areas of tick exposure for humans, promote the transmission of tick-borne pathogens and increases the number of human patients (Beugnet and Marié, 2009; Nicholson, 2010; Rizzoli et al., 2014). Beside these environmental changes leading to increased hazard exposure to well-known vector-borne pathogens, increased clinician awareness, new diagnostic tools, improved surveillance and increased reporting and communication of tick-borne diseases in several countries can also explain the increased incidence of some tick-borne diseases (Baneth, 2014; Doulier et al., 2010; Folkema et al., 2012; Heyman et al., 2010).

Finally, advances in molecular biology allow the discovery of new species, strains or genetic variants and extend the list of microorganisms able to infect either animals or humans or both (Baneth, 2014; Doulier et al., 2010; Rizzoli et al., 2014). Therefore, TBDs are increasingly recognized as rising hazard for public health (Rizzoli et al., 2014). These observations are particularly obvious for *A. phagocytophilum*. Indeed, the environment suitability of *Ixodes scapularis* and *I. pacificus*, the main vectors for *B. burgdorferi* and *A. phagocytophilum*, seems to increase in Canada (Villeneuve et al., 2011). Furthermore, high prevalences of *A. phagocytophilum* in ticks have been recorded several in European countries (Rizzoli et al., 2014) and its prevalence is increasing in both animals and humans (CDC, 2008; Folkema et al., 2012; Heikkinä et al., 2010). In the USA, both canine and human exposure has progressively increased from 2008 to 2010 and from 2009 to 2010 respectively. The number of reported human cases has increased by 53% during this period (Qurollo et al., 2014).

**Description of the pathogen Anaplasma phagocytophilum**

*Anaplasma phagocytophilum* is an obligate intracellular gram-negative tick-borne rickettsialae bacterium of worldwide distribution (Berzina et al., 2013; Diniz and Breitscherdt, 2012; Dumler et al., 2005; Keesing et al., 2014). The name of *A. phagocytophilum* has been given in 2001 to merge three previously distinct agents, the agent of equine granulocytic anaplasmosis or previously ehrlichiosis (*E. equi*), the agent of tick borne fever or pasture fever in sheep and cattle (*E. phagocytophila*) and the agent of human granulocytic anaplasmosis (previously human ehrlichiosis) (Dumler et al., 2001).

This bacterium belongs to the family of *Anaplasmataceae* in the order of *Rickettsiales* (Alleman and Wamsley, 2008; Woldehiwet, 2010). The family *Anaplasmataceae* includes obligate intracellular arthropod-borne *a*-proteobacteria responsible of endemic and emerging diseases of major relevance in both veterinary and human medicine with important economic and public health outcomes (Pruneau et al., 2014). More specifically, *Anaplasma* and *Ehrlichia* genera include tick-borne pathogens that mostly infect peripheral blood cells (Dumler et al., 2005). Indeed, *A. phagocytophilum* infects myeloid cells of bone marrow, mainly neutrophils but also occasionnaly eosinophils. This organism develops within intracytoplasmic inclusions of varying size (from 1.5 to 6 mm in diameter) and derived from the host cell membrane called “morula” (from Latin morum “mulberry”) (Figure 1) (Diniz and Breitscherdt, 2012; Dumler et al., 2005; Woldehiwet, 2010).

![Figure 1: Morulae of *A. phagocytophilum* morula (black arrows) within a canine neutrophil, Wright's stain, ×100 (A) (Carrade et al., 2009) and in neutrophil of a 65-year-old man with a 2-day history of fever and diarrhea, Wright stain, ×100 (B) (Weil et al., 2012).](image-url)
A. phagocytophilum causes a zoonotic disease called granulocytic anaplasmosis (Beugnet and Marié, 2009; Dumler et al., 2005; Keesing et al., 2014). Before the mid 1990s and the discovery of the first cases of human granulocytic anaplasmosis (formerly human granulocytic ehrlichiosis) in Wisconsin, A. phagocytophilum was thought to infect only domestic animals and free-living reservoirs (Cochez et al., 2011; Dumler et al., 2005; Kybicová, 2010).

Epidemiological features of A. phagocytophilum

Geographic distribution

A. phagocytophilum infection in both people and domestic animals has a worldwide geographic distribution that commonly follows the distribution of its vector, Ixodes spp ticks (Diniz and Breitschwerdt, 2012; Dumler et al., 2007). Although A. phagocytophilum has been identified in several countries, the endemic areas include the upper Midwest, New England, western coast especially northern California, eastern and northeastern regions of the USA, British Colombia and some central and northern European countries (Sainz et al., 2015; Swanson et al., 2006; Keesing et al., 2014). The organism has also been reported in Scandinavia, Baltic countries (Latvia, Lithuania, and Estonia), Finland, Asia, South America and North Africa (Bertzina et al., 2013). However, data are lacking in large areas including parts of Asia, Africa, Latin America and Oceania (Swanson et al., 2006). In North Africa, only few data have been recently published in Tunisia, Algeria and Egypt (Azzag et al., 2015; Ben Said et al., 2014; Ghafar and Amer, 2012; M’ghirbi et al., 2009; M’ghirbi et al., 2012).

Vector

A. phagocytophilum is defined as a tick-borne disease, contamination of people and domestic animal occurs mostly after tick bites especially when they come in contact with the vector in host reservoir habitat (Diniz and Breitschwerdt, 2012; Leiby et al., 2002). The bacterium is transmitted most frequently by ticks of Ixodes persulcatus complex (Stuen et al., 2013; Swanson et al., 2006). Ticks included in this complex are involved in the transmission of the majority of Ixodes-vectored human diseases and the most important species are I. scapularis, I. pacificus, I. ricinus and I. persulcatus (Swanson et al., 2006). These ticks have a worldwide distribution but are mainly encountered in the northern hemisphere (Figure 2) (Swanson et al., 2006; Woldehiwet, 2010).

Ixodes species involved in the transmission of the bacterium varies according to the geographic area (Figure 2). In the United States, the main vectors are I. scapularis (blacklegged or deer tick) and I. pacificus (western-blacklegged tick) (Figure 3) (Doudier et al., 2010; Jin et al., 2012). In Europe, especially in Northwestern areas, the most common vector is I. ricinus (sheep or castor bean tick) (Figure 3) (Jin et al., 2012; Swanson et al., 2006). Some authors considered that this tick is the only vector of A. phagocytophilum in Europe (Heyman et al., 2010; Sainz et al., 2015). I. persulcatus tick (Figure 3) is also present in some European regions especially eastern parts, and can share some areas with I. ricinus (Figure 2). This tick species has a geographic area that extends into Japan and is considered the primary vector in Asia (Sainz et al., 2015; Swanson et al., 2006). In eastern Mediterranean areas and North Africa, ticks of Rhipicephalus, Haemaphysalis, and Ixodes genera are also involved in the transmission of the bacterium (Ghafar and Amer, 2012; Qablan et al., 2012; M’ghirbi et al., 2012; Sarih et al., 2005). A wide variety of other tick species were found to be positive to A. phagocytophilum in the USA, Europe and Asia including other Ixodes spp., Amblyomma americanum, Dermacentor spp., (Doudier et al., 2010; Jin et al., 2012; Stuen et al., 2013).

Figure 2: Worldwide geographic distributions of Ixodes tick species, vectors of A. phagocytophilum (Adapted from Swanson et al. 2006)
**Ixodes scapularis**  
Blacklegged tick  
Deer tick

**Ixodes pacificus**  
Western-blacklegged tick

**Ixodes ricinus**  
Sheep tick  
Castor bean tick

**Ixodes persulcatus**

**Rhipicephalus sanguineus**

*Figure 3: Ticks involved in the transmission of *A. phagocytophilum* in the USA, Europe, Asia and the Mediterranean region. *I. scapularis*, *I. pacificus*, *R. sanguineus* (TickEncounter Resource Center of the University of Rhode Island), *I. ricinus* (Stanek et al. 2012), tick developmental stages and *I. persulcatus* (Online photographic guide to ticks, Bristol University tick ID).*
**Reservoir hosts**

The absence of transovarian transmission in the vector makes it unable to act as a reservoir of *A. phagocytophilum*. Although a wide range of animal species can be infected by the bacterium, hosts might fulfill several characteristics to be considered as competent reservoir. Indeed, a host reservoir must be fed on by an infected vector tick at least occasionally, take up a critical number of the infectious agent during the bite by an infected tick, allow the pathogen to multiply and survive for a period in at least some parts of his body and might allow the pathogen to find its way into other feeding ticks (Rizzoli et al., 2014; Stuen et al., 2013). Several mammalian species are considered as host reservoir and thus, enable the persistence of the bacterium between seasons of tick activity and its spread through their movement in case of migratory animals (Stuen et al., 2013). Among them, rodents and wild cervids are considered to be the principal host reservoir of the bacterium (Alleman and Wamsley, 2008; Beugnet and Marié, 2009; Nicholson et al., 2010).

In Europe, even though *A. phagocytophilum* has been detected in a wide range of wild animal species, the reservoir host for the human pathogenic strain is still unknown (Heyman et al., 2010; Michalik et al., 2012; Strasek Smrdel et al., 2013). Indeed, the reservoir competence of rodents is not established and cervids are reported to disseminate mainly variants that have not been isolated in humans with possible exception for red deer (Michalik et al., 2012). Similarly, no information is available on the reservoir hosts competence of wild animals for *A. phagocytophilum* in Asia (Cao et al., 2006). Only few studies have been carried and showed relatively high prevalence rates of infection by *A. phagocytophilum* in wild ruminants and small mammals (Stuen et al., 2013). *A. phagocytophilum* has been also detected in several other wild vertebrates including boar, fox, bear, European bison, donkey, moose, hare, Eurasian lynx, birds and reptiles (Kybicová, 2010; Stuen et al., 2013). However, their role in the bacterium life cycle is not assessed (Stuen et al., 2013). In some geographical areas, several bird species are thought to be either competent host reservoirs of the bacterium or to contribute to the circulation and spread of infected ticks (Diniz and Breitschwerdt, 2012; Little, 2012; Woldehiwet, 2010).

**Life cycle of *A. phagocytophilum* transmission by Ixodes tick species**

*A. phagocytophilum* is considered to be naturally maintained in a tick-rodent cycle (Figure 4) (Cao et al., 2006). The interaction between reservoir hosts and tick-borne pathogens is variable and has a direct impact on transmission dynamics. In the case of bacterial tick-borne infections that often lead to an immune system response in the host reservoir or to its death limiting the bacteremia phase, ticks represent a critical feature for the maintenance of the enzootic cycle in nature. The perpetuation of cycles can be ensured either by the transmission of the pathogens between different tick development stages (transstadial transmission), or between generation (transovarian transmission) or between ticks during cofeeding (Swanson et al., 2006).

The life cycle of *Ixodes* ticks lasts for almost 2 years (Littman et al., 2006; Swanson et al., 2006) and its duration depends on climatic conditions varying from less than a year in tropical regions to three or more years in temperate regions (Heyman et al., 2010). This life cycle comprises four distinct developmental stages: egg, larva, nymph and adult. *Ixodes* ticks activity varies according to the life stage and they mostly quest on vegetation in prime suburban real estate (Littman et al., 2006; Swanson et al., 2006). The feeding behavior at each life stage has a direct effect on the risk of tick-borne pathogens transmission (Swanson et al., 2006). All *Ixodes* species of public health relevance need to feed on a new host at each life stage after hatching and the blood meal is completed in three to five days (Heyman et al., 2010; Swanson et al., 2006). Ticks belonging to *I. persulcatus* complex are exophilic, anthropophilic and nonspecific feeding ticks. Consequently, they can have their blood meal on both various host reservoirs and on humans (Stuen et al., 2013; Swanson et al., 2006).

*A. phagocytophilum* is transmitted to the host during the bite of a nymphal or adult tick infected during previous stages (larval or nymphal) (Diniz and Breitschwerdt, 2012; Doudier et al., 2010; Nicholson et al., 2010) (Figure 4). Transmission of *A. phagocytophilum* to the host during tick feeding occurs usually within 24 to 48 h. Consequently, at least daily removal of ticks should be recommended in association with ectoparasites preventive treatment in endemic areas to avoid the transmission of the bacterium (Cockwill et al., 2009). As nymphs have very small size (approximately 1 mm), they are often able to feed much longer and are at increased risk to transmit tick-borne pathogens such as *A. phagocytophilum* (Heyman et al., 2010; Swanson et al., 2006). In contrast, adult ticks are bigger making them more quickly detectable and removed before disease transmission (Swanson et al., 2006). Due to the transstadial transmission, nymphs and adult ticks contaminated in a previous stage last infected after molting and are able to contaminate susceptible hosts during the following blood meals.

Adult female ticks require an additional feeding to develop their egg (Heyman et al., 2010; Swanson et al., 2006). This additional blood meal could explain the higher prevalence of *A. phagocytophilum* in adult ticks reported in some studies (Stuen et al., 2013). As *A. phagocytophilum* is not transmitted transovarially among *Ixodes* ticks (Doudier et al., 2005; Stuen et al., 2013; Swanson et al., 2006), larvae are mostly considered free from infection until hatching and having their first blood meal (Doudier et al., 2010; Swanson et al., 2006). Another consequence of the absence of transovarial transmission is that when adult femal tick laid their eggs, the bacterial cycle is interrupted (Bakken and Dumler, 2008; Stuen et al., 2013).
A. phagocytophilum: A zoonotic pathogen of veterinary and public health importance

A large variety of mammals are receptive to A. phagocytophilum. However, the disease has been described only in dogs, horses, cattle, sheep, goats, llamas, cats and humans (Eberts et al., 2011; Gorna et al., 2013; Mazepa et al., 2010). People and domestic animals are considered incidental hosts (Poitout et al., 2005).

In domestic ruminants

A. phagocytophilum was first described in domestic ruminants including sheep, goat, deer and cattle (Carrade et al., 2009; Jin et al., 2012; Woldehiwet, 2010). The disease was named tick-borne fever (TBF) in ruminants and was first described in sheep in Scotland in 1932 (Cochez et al., 2011; Jin et al., 2012). Later in the 1950s, the bacterium was identified as the causative agent of pasture fever in cattle in England (Beugnet and Marié, 2009). Then, A. phagocytophilum has been reported in sheep and cattle with TBF in several countries of Europe including Ireland, Scandinavia, Netherlands, Austria, Switzerland and Spain (Beugnet and Marié, 2009; Woldehiwet, 2010). Recently, the organism has also been identified in camels (Ben Said et al., 2014; Carrade et al., 2009; Mentaberre et al., 2013).

Two recent studies that investigated the prevalence of A. phagocytophilum in Tunisia and Canaries Islands found a prevalence of 29.2 and 3% respectively (Ben Said et al., 2014; Mentaberre et al., 2013). The disease, also called bovine ehrlichiosis, is mostly described in spring and autumn in animals grazing in favorable biotopes for ticks (Guyot et al., 2011). Clinical signs associated with TBF and pasture fever include a sudden onset of high fever, anorexia, dullness, arthritis, oedema of legs and weight loss. Less frequently, cutaneous and mucous membrane hemorrhage were also described (Ben Said et al., 2014; Guyot et al., 2011; Stuen et al., 2013).

A. phagocytophilum infection can also induce immune deficiency in ruminants (Ben Said et al., 2013; Guyot et al., 2011) leading to secondary opportunistic infections such as Staphylococcus aureus, Pasteurella spp. and Listeria monocytogenes infections (Carrade et al., 2009). The severity of fever varies according to the age of the animal, the variant involved, the host species and the immunological status of the individual affected. Young animals and tick-free individuals placed on infested pasture seem to be the most sensitive to A. phagocytophilum infection (Stuen et al., 2013). In addition, the disease is considered to be a cause of important productivity loss in dairy cattle including drop in milk yield, reduced weight gain in infected bullocks and lambs, reduced fertility and abortions (Ben Said et al., 2014; Beugnet and Marié, 2009; Stuen et al., 2013).

In horses

The disease was initially known as equine granulocytic ehrlichiosis (EGE) and was first reported in California in the late 1960s (M’ghirbi et al., 2012; Pusterla and Madigan, 2013). Other cases were then described in several parts of Europe and America including Scandinavia, Switzerland, the United Kingdom, France, Brazil, Canada, Florida, Washington, Oregon, New York, Colorado, Illinois, Minnesota, Indiana, Wisconsin, New Jersey and Connecticut (Beugnet and Marié, 2009; Pusterla and Madigan, 2013; Woldehiwet, 2010). In Europe, the seroreactivity to A. phagocytophilum in horses has been assessed in several countries and varies from 6.52 to 22.3% (M’ghirbi et al., 2012).

A recent study carried out on 60 horses living in regions favorable to I. ricinus tick in Tunisia revealed a prevalence of 67 and 13% by serology and PCR respectively. The prevalence by PCR is similar to reported rates in Italy (M’ghirbi et al., 2012). Equine granulocytic anaplasmosis is described as an acute disease with an estimated incubation period of less than two weeks. The disease in mainly characterized by fever, lethargy, inappetence, staggering or ataxia, distal limb edema, reluctance to move and icterus (Franzen et al., 2009; M’ghirbi et al., 2012; Pusterla and Madigan, 2013). Occasionally, cardiac arrhythmia is reported including ventricular tachycardia and premature ventricular contractions and are possibly due to myocardial vasculitis (Pusterla and Madigan, 2013). Clinical presentation is unspecific like in other animal species and mimics other infectious diseases including Lyme disease, leptospirosis, babesiosis, theileriosis, equine herpes virus and equine infectious anemia virus (M’ghirbi et al., 2012). These clinical signs can also be associated with hematomatological modifications including thrombocytopenia, leucopenia, neutropenia, lymphopenia and mild anemia. The evolution is mostly favorable, even without treatment, with recovery several weeks after the onset of symptoms (Franzen et al., 2009; M’ghirbi et al., 2012; Pusterla and Madigan, 2013). Indeed, subclinical infections are estimated to reach up to 50% of equine cases and thus the disease seems largely underestimated in most endemic European countries (M’ghirbi et al., 2012). However, fatalities exist and can be due to opportunistic infections or traumatic injuries secondary to the lack of coordination (Pusterla and Madigan, 2013).

The severity of the diseases varies according to the age with horses less than 1 year old displaying limited clinical signs, those younger than 4 years old developing mild clinical signs and those older than 4 years old develop progressive characteristic disease (Pusterla and Madigan, 2013).
The duration of the disease varies from 3 to 16 days. During natural infection, the peak of antibody titer occurs 19 to 81 days after the onset of clinical signs. Immunity seems to be protective and lasts for at least 2 years (M’ghirbi et al., 2012; Pusterla and Madigan, 2013). In experimentally infected horses, antibody titer starts to progressively decline 300 days post-infection unless reinfection occurs (M’ghirbi et al., 2012).

In companion animals (cats and dogs)

A. phagocytophilum infection was recognized in the first time in dogs in 1982 in California (Little, 2012; Woldehiwet, 2010). The disease has been described in several states of the USA but also in Europe as soon as the late 1980s (Beugnet and Marié, 2009; Carrade et al., 2009). Most dogs infected by A. phagocytophilum remain apparently healthy. This is suggested by the discrepancy between the high seroprevalence and the relative low number of sick dogs in endemic areas (Carrade et al., 2009; Diniz and Breitschwerdt, 2012; Ravnick et al., 2014). Therefore, most immuno-competent dogs seem to control this infection and thus develop a subclinical or mild and self-limiting disease (Diniz and Breitschwerdt, 2012). However, some dogs infected by A. phagocytophilum develop an unpecific illness mostly characterized by an acute onset of fever, lethargy, depression, decreased appetite or anorexia, weight loss and musculoskeletal pain or discomfort (Beugnet and Marié, 2009; Carrade et al., 2009; Diniz and Breitschwerdt, 2012). Lymphadenopathy, splenomegaly and hepatomegaly are also frequently described (Diniz and Breitschwerdt, 2012; Little, 2012). Less frequent clinical signs include digestive signs, polyuria, polydipsia, respiratory signs, pale mucous membranes, hemorrhagic diathesis, collapse, uveitis, scleral congestion, endocarditis, polymyositis and neurological signs (Carrade et al., 2009; Cockwill et al., 2009; Diniz and Breitschwerdt, 2012; Mazepa et al., 2010; Ravnik et al., 2011; Silaghi et al., 2011).

Most important hematological and serum biochemistry profile modifications associated with canine granulocytic anaplasmosis include thrombocytopenia, mild to moderate nonregenerative normocytic normochromic and increased liver enzymes activity (Carrade et al., 2009; Diniz and Breitschwerdt, 2012; Kohn et al., 2008; Silaghi et al., 2011). The severity of the disease is variable, from a subclinical infection to an acute form with severe clinical presentation (Poitout et al., 2005; Ravnik et al., 2011). The variability of the severity of clinical signs can be due either to the presence of co-infections, the immune response of the host or the virulence of strains/variants (Carrade et al., 2009; Diniz and Breitschwerdt, 2012; Mazepa et al., 2010). The prognosis of the disease in dogs is usually favorable with a rapid remission after doxycycline therapy (Mazepa et al., 2010; Ravnick et al., 2014). However, few fatality cases are reported (Bexfield et al., 2005; Kohn et al., 2008; Mazepa et al., 2010).

More recent experimental studies have shown that cats are also susceptible to the infection by A. phagocytophilum. The first case in feline species was reported in the late 1990s (Beugnet and Marié, 2009; Lappin et al., 2012; Little, 2012). Then only few reports described feline cases of granulocytic anaplasmosis in European countries including Sweden, Switzerland, Finland and Italy (Gorna et al., 2013). Even though granulocytic anaplasmosis is increasingly diagnosed all over the world, the disease seems to be rarely identified among cats. This can be due to their particular behavior that can remove ticks during grooming or to differences in the pathogenesis of the disease in this species (Gorna et al., 2013; Heikkilä et al., 2010).

In cats, the bacterium causes clinical signs similar to those described in dogs including fever, lameness, enlarged lymph nodes, lethargy, tachypnoea, anorexia and weight loss (Heikkilä et al., 2010; Lappin et al., 2012; Little, 2012). Periodontal disease, gingivitis, vomiting, abdominal pain, pharyngitis, polydipsia, hematuria, muscle and joint pain, conjunctivitis and neurologic signs including hyperesthesia, tremors, incoordination and shyness have also been reported (Gorna et al., 2013; Heikkilä et al., 2010; Little, 2012). However, whether these symptoms are attributed to anaplasmosis or to opportunistic infections secondary to an immune deficiency associated with A. phagocytophilum infection is unknown (Heikkilä et al., 2010). Like in dogs, these clinical signs are often accompanied by hematological and biochemical abnormalities including thrombocytopenia, lymphopenia, neutrophilia with a left shift, anemia, monoclonal gammopathy, and increased liver enzymes activity (Gorna et al., 2013; Heikkilä et al., 2010; Lappin et al., 2012). Thrombocytopenia is the most common hematological abnormality like described in other species and is mild to moderate in cats (Heikkilä et al., 2010).

In humans

Currently, human granulocytic anaplasmosis (HGA) is considered to be the third most important vector-borne disease in both the USA and Europe and is also increasingly diagnosed in some Asian countries (Dumler, 2012; Li et al., 2011; Zhang et al., 2008). In the USA, anaplasmosis is a nationally notifiable disease (Bakken and Dumler, 2008; CDC, 2008) and the number of cases has critically and rapidly increased (Figure 5). Between 2000 and 2010, incidence has increased from 1.4 to 6.1 cases per million inhabitants (Dahlgren et al., 2011; Rizzoli et al., 2014).

![Figure 5: Number of annual human granulocytic anaplasmosis cases in the USA from 1994 to 2010](http://www.cdc.gov/anaplasmosis/stats/)
HGA is an unspecified flu-like illness mostly characterized by fever, headache, chills, myalgia and malaise (Dumler, 2012; Folkema et al., 2012; Rymaszewska and Adamska, 2011). Symptoms usually appear ten days to three weeks after tick bite (Heyman et al., 2010; Stuen et al., 2013). In most cases, clinical signs are mild and self-limited, with favorable evolution even without treatment (Cochez et al., 2011; Jin et al., 2012). However, some patients can develop severe life-threatening complications (Cochez et al., 2011; Dumler, 2012; Jin et al., 2012). Due to the potential serious outcomes associated with the disease, the Infectious diseases Society of America recommends to give antimicrobial therapy to every person suspected to have HGA on the basis of clinical presentation although mild or self-limiting pending the laboratory results and to do not delay the treatment (Heyman et al., 2010).

CONCLUSION

Although *A. phagocytophilum* is known as a veterinary pathogen causing disease in ruminants since more than 70 years, its zoonotic potential is more recently recognized. The ability of causing disease in humans with potential severe outcomes, the worldwide distribution and the rising focus on ticks and tick-borne diseases increased physician interest and awareness on this emerging pathogen. The difficulty of diagnosis either in human or in veterinary medicine and the importance of giving early treatment to avoid severe complications highlight the importance of improved knowledge on this pathogen especially epidemiological information. Epidemiological data are also crucial to perform effective preventive strategies. Although the number of publications on *A. phagocytophilum* and granulocytic anaplasmosis is important and increasing, several data are still missing including epidemiological informations in huge parts of Asia, Latin America and Africa and implications of strain variability in the pathogenicity of the disease. Several works on this pathogen are ongoing in Morocco in ruminants, dogs, ticks and humans in order to elucidate mechanisms of transmission and epidemiological context on this infection.

REFERENCES


