Tick-borne bacterial diseases emerging in Europe

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Since the identification of *Borrelia burgdorferi* as the agent of Lyme disease in 1982, 11 tick-borne human bacterial pathogens have been described throughout Europe. These include five spotted fever rickettsiae, the agent of human granulocytic ehrlichiosis, four species of the *B. burgdorferi* complex and a new relapsing fever borrelia. We present these emerging diseases and focus on the factors that play a role in the recognition of new tick-borne diseases.

Keywords Ticks, Europe, rickettsia, borrelia, ehrlichia, emerging diseases

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Ticks are obligate hematophagous acarins that parasitize every class of vertebrate throughout the world and may bite people [1]. Since the beginning of the century, ticks have been described as vectors of human diseases, including bacterial (spotted fever rickettsioses, recurrent fever borrelioses, tularemia, Q fever) [2,3], viral [3,4] and protozoan [3,5] zoonoses. However, the major impact of ticks on public health was recognized with the identification and emergence of *B. burgdorferi* as the etiologic agent of Lyme disease in 1982, which brought the subject to general attention. Currently, there is an increasing awareness of tick-borne diseases, and efforts of both clinicians and researchers have led to the recent description of emerging tick-borne bacterial diseases, particularly in Europe (Figure 1).

Each tick species that may act as a vector favors particular optimal environmental conditions and biotopes. These determine the geographic distribution of the ticks and consequently the risk area for tick-borne diseases. This is particularly true when ticks are not only vectors, but also reservoirs of pathogens; this is the case for rickettsioses. The Mediterranean spotted fever ('boutonneuse' fever) caused by *Rickettsia conorii* and transmitted by the brown dog tick *Rhipicephalus sanguineus* is encountered in summer in the Mediterranean area. Until recently it was thought to be the only rickettsiosis prevalent in Europe. The onset of signs is abrupt, and typical cases have a high fever, a rash and a unique eschar (the 'tache noire') at the tick bite site [6]. However, five newly recognized tick-borne rickettsioses have been described throughout Europe during the past 9 years. In 1991, the causative agent of Astrakhan fever was described as a rickettsia closely related to, but distinct from, *Rickettsia conorii*. The suspected vector of this eruptive summer disease occurring in Astrakhan on the Caspian Sea is the dog tick *Rhipicephalus pumilio* [6]. In March 1996, a 63-year-old woman from Marseille presented with a fever, a discrete rash and an eschar in her left groin. A rickettsia previously isolated from *Hyalomma asiaticum* ticks in Mongolia was obtained from the blood and the skin of the patient. She had no previous travel history, and risk factors for tick bites included only the collection of compost from a garden where migratory birds were resting. It was hypothesized that the birds could have transported the rickettsia, and the name *Rickettsia mongolotimonae* was proposed [7]. A second case was described in May 1998 in an HIV patient who had been gardening in a rural area of Marseille. This patient presented with fever, headache, an eschar, lymphangitis and painful satellite lymphadenopathy [8]. Since then, two other cases have been documented in southern France, and *Rickettsia mongolotimonae* has been detected in *Hyalomma truncatum* collected from cattle in sub-Saharan Africa (unpublished data). Thus, *Rickettsia mongolotimonae* may be specifically associated with *Hyalomma* sp. ticks. In southern France, the vector has yet to be described, but *Hyalomma* spp. are known to parasitize birds and mammals in this area.

In 1997, the first documented case of infection due to *Rickettsia slovaca* was reported in a woman bitten by *Dermacentor marginatus* in France [9]. The woman had presented with fever and an eschar at the site of the tick's attachment on the scalp, which was surrounded by an extensive erythema. She also had enlarged cervical lymph nodes and suffered from fatigue.

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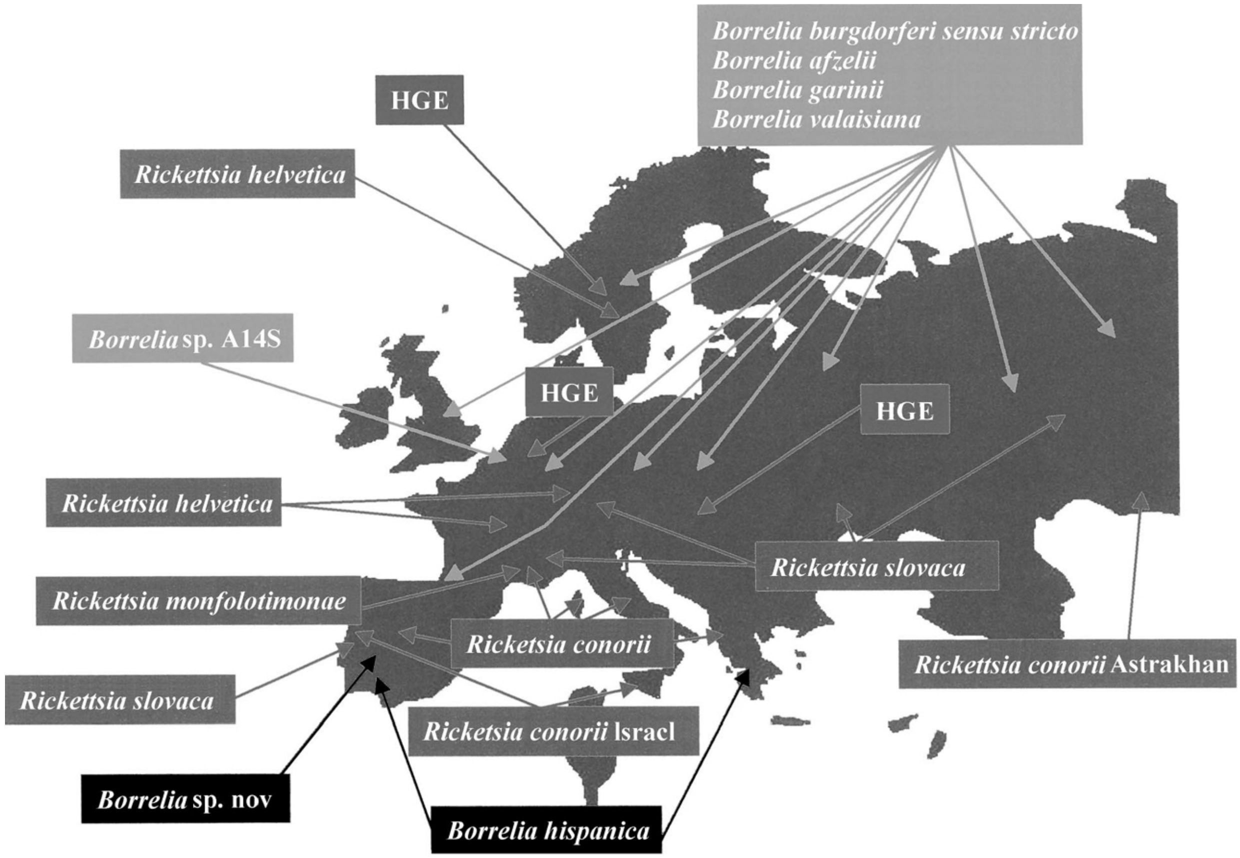

Figure 1 Geographic distribution of tick-borne rickettsioses, ehrlichioses and borrelioses in Europe. *B. valaisiana* is strongly suspected to be a pathogen.

Similar undocumented cases had previously been reported in France, Slovakia and Hungary, where this clinical syndrome was known as 'Tibola' (for tick-borne lymphadenopathy). *Rickettsia slovaca* was found in all European countries where *D. marginatus* was screened for rickettsial infections, including France, Switzerland, Slovakia, Ukraine, Yugoslavia, Armenia and Portugal [10]. To date, 25 cases have been documented in patients from France and Hungary presenting with tick bites on the scalp and lymphadenopathy (unpublished data). Fever is uncommon, and sequelae include localized alopecia at the bite site and chronic fatigue. *D. marginatus* and *D. reticulatus* are potential vectors. Both species are prevalent throughout Europe to central Asia (except for *D. marginatus*, which has not been identified in northern Europe). Adult ticks inhabit forests and pastures. They may feed on humans and frequently bite the scalp. They are active during early spring, again in autumn and even in winter in southern Europe.

More recently, *Rickettsia helvetica* was implicated in 1999 in fatal perimyocarditis in young patients in Sweden [11]. This bacterium was detected by PCR in the pericardium and in a lymph node from the pulmonary hilum in the first patient, and in a coronary artery and the heart muscle in the second patient. Electron microscopy yielded a rickettsia-like organism predominantly located in the endothelium, and the patients' sera reacted with spotted fever group rickettsia antigens. We also reported the case of a French patient who seroconverted against *Rickettsia helvetica* 4 weeks after the onset of an unexplained febrile illness [12]. The vector is *Ixodes ricinus*, which is also the vector of Lyme borreliosis and distributed throughout Europe, particularly in forests. In addition, we recently described a seroprevalence of 9.2% against *Rickettsia helvetica* among forest workers from the area where the patient lived. More recently, in 1999 Israeli spotted fever caused by a rickettsia closely related to *Rickettsia conorii* and which is known to occur in Israel was identified in Sicily and Portugal [13]. It is transmitted by *Rhipicephalus sanguineus*. The inoculation eschar is usually lacking and the disease may be severe. Finally, European clinicians have to consider the new rickettsioses described throughout the world that may present as imported diseases, particularly African tick bite fever caused by *Rickettsia africae* in patients returning from sub-Saharan Africa or the West Indies [14,15]. In a prospective study conducted among more than 800 Norwegian travelers returning from rural Africa, around 3% had clinical signs and serologic tests consistent with African tick bite fever (M. Jensenius, unpublished data).

In recent years, human granulocytic ehrlichiosis (HGE) has also emerged in Europe. This disease was first described in the USA in 1994 and presents most commonly as an undifferentiated, febrile, potentially severe illness occurring in summer or spring [16]. The causative organism is very closely related to *Ehrlichia equi* and *E. phagocytophila* (pathogens of horses and ruminants, respectively). Although seroepidemiologic studies led to the suspicion that HGE occurs in most European countries with a prevalence of 0–2% in blood donors and 5–25% of tick-exposed people, the first documented case was reported in Slovenia in 1997 [17]. Since then, six cases have been confirmed in Slovenia, three in Sweden, and one in The Netherlands, and serologically documented cases have been reported in Spain [18–20]. The tick vector of HGE in Europe is *Ixodes ricinus*. Small mammals, in particular *Apodemus sylvaticus* (wood mouse), *Apodemus flavicollis* (yellow-necked mouse), *Sorex araneus* (common shrew) and *Clethrinomys glareolus* (bank vole), have recently been implicated as reservoirs of granulocytic ehrlichiae in Europe [21]. To date, there are no convincing reports on the presence in Europe of the two other known human ehrlichioses, including the human monocytic ehrlichiosis caused by *E. chaffeensis* and the infection caused by *E. ewingii*, which have been described in the USA [16,22].

New data have also been obtained on tick-borne borrelioses. Lyme borreliosis is caused by three of the 10 described species in the *B. burgdoferi* sensu lato complex: *B. burgdorferi* sensu stricto, *B. garinii* and *B. afzelli*. Differences appeared in the organotropism of these *Borrelia* species. *B. afzelii* is associated with erythema migrans and a milder disease than that caused by *B. burgdorferi* sensu stricto. It is also the principal cause of acrodermatitis chronica atrophicans and a cause of borrelial lymphocytoma. Infections with *B. garinii* are more frequently associated with neurologic forms of the diseases, while those with *B. burgdorferi* sensu stricto are more often associated with rheumatologic disorders [23]. In Europe, *Apodemus* species are considered to be the most important reservoirs of the bacteria. Various species of birds, especially ground-foraging birds, have also been incriminated as reservoirs. Although each pathogenic species of *Borrelia* has been found to be associated with birds in Europe, *B. afzelii* is thought to be perpetuated in rodents and *B. garinii* in avian reservoir hosts [24]. Recently, a novel isolate (A14S) of the *B. burgdoferi* sensu lato complex has been detected from a skin biopsy of a patient with erythema migrans in The Netherlands [25]. Furthermore, a pathogenic role for *B. valaisiana* that occurs in Europe and Asia is suspected [26]. Finally, although relapsing fever borrelioses transmitted by soft ticks of the genus *Ornithodoros* have long been recognized as human diseases, some species, including the African *B. duttonii* and *B. crocidurae*, have only recently been cultured. In southern Europe, recurrent fever due to *B. hispanica* is reported sporadically, and a new species pathogenic to humans was isolated and characterized in Spain in 1996 [27].

The increase in outdoor activities among Europeans has resulted in increased contact with ticks and increased risk of transmitted diseases. However, numerous factors are playing a role in the recognition of new tick-borne diseases. Although serology is of most value in the diagnosis of a tick-borne disease, a major limitation is cross-reactivity [28]. For example, it is frequently not possible to differentiate among spotted fever rickettsiae or granulocytic ehrlichiae. The development of new techniques, including the shell-vial assay for the isolation of organisms and molecular methods for their characterization, has improved the specific diagnosis of tick-borne bacterial diseases. Methods based on PCR gene amplification have made possible the development of useful, sensitive and rapid tools to detect and identify tick-borne pathogens from blood, ticks and skin biopsy specimens [2,29]. It is relatively simple for a laboratory to detect and identify bacteria (including new strains) if there are facilities for molecular methods and access to sequence data. Modern diagnostic methods combined with the curiosity of clinicians about atypical cases are the keys to the recognition of new diseases.

For example, Astrakhan fever was found in an area where spotted fever group rickettsiae were not known to occur. The presence of an inoculation eschar in patients presenting with an eruptive febrile disease led to the suspicion of a rickettsiosis. Although some physicians in Astrakhan were doubtful about this hypothesis, it was proved by the use of a modern cell-culture system and molecular tools in Moscow. Moreover, the study of atypical cases in France, where *Rickettsia conorii* was thought to be the only pathogenic rickettsia, led to the recognition of the pathogenicity of *Rickettsia mongolotimonae*. The patient presented in March, an atypical month for Mediterranean spotted fever, and molecular methods were critical in incriminating this bacterium, which had previously been detected in ticks only. These methods also contributed to the description of new clinical syndromes caused by organisms that had previously been considered as 'rickettsiae of unknown pathogenicity', including *Rickettsia slovaca* and *Rickettsia helvetica*.

To date, numbers of rickettsiae, borreliae, ehrlichiae and even bartonellae have been found in ticks only [6,30]. Their pathogenicity in people is yet to be determined, but they represent potential candidates for new tick-borne diseases to be described in the future. The public has to be informed about the avoidance of tick-infested areas and about measures that are known to decrease the risk of tick bites, including the use of tick repellents [2]. Physicians must keep in mind the importance of promptly treating patients presenting with acute febrile illnesses after tick bites. Doxycycline is effective against all known bacterial pathogens transmitted by ticks and should be started in symptomatic patients before the diagnostic results [2].

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