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Rickettsioses in Europe

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Abstract

Bacteria of the genera *Rickettsia* and *Orientia* (family *rickettsiaceae*, order r*ickettsiales*) cause rickettsioses worldwide, and are transmitted by lice, fleas, ticks and mites. In Europe, only *Rickettsia* spp. cause rickettsioses.

With improvement of hygiene, the risk of louse-borne rickettsiosis (epidemic typhus) is low in Europe. Nevertheless, recrudescent form of *Rickettsia prowazekii* infection persists. There could be an epidemic typhus outbreak if a body lice epidemic occurs under unfavorable sanitary conditions.

In Europe, endemic typhus or *Rickettsia typhi* infection, transmitted by rats and fleas, causes febrile illness. At the beginning of this century, flea-borne spotted fever cases caused by *Rickettsia felis* were diagnosed. Flea-borne rickettsiosis should be suspected after flea bites if fever, with or without rash, is developed.

Tick-borne rickettsioses are the main source of rickettsia infections in Europe. Apart from *Rickettsia conorii*, the Mediterranean Spotted Fever (MSF) agent, other *Rickettsia* spp. cause MSF-like: *Rickettsia helvetica*, *Rickettsia monacensis*, *Rickettsia massiliae* or *Rickettsia aeschlimannii*. In the 1990s, two 'new' rickettsioses were diagnosed: Lymphangitis Associated Rickettsiosis (LAR) caused by *Rickettsia sibirica mongolitimonae*, and Tick-Borne Lymphadenopathy/*Dermacentor*-Borne-Necrosis-Erythema-Lymphadenopathy/Scalp Eschar Neck Lymphadenopathy (TIBOLA/DEBONEL/SENLAT), caused by *Rickettsia slovaca*, *Candidatus* Rickettsia rioja and *Rickettsia raoultii*.

Lastly, European reports about mite-borne rickettsiosis are scarce.

Keywords: Lice; Fleas; Ticks; Mites; Rickettsiosis; Europe; Typhus; MSF; LAR; DEBONEL/TIBOLA/SENLAT; Rickettsialpox

1. Introduction

Rickettsioses are worldwide zoonoses caused by bacteria (Genera *Rickettsia* and *Orientia*) belonging to α1-proteobacteria and transmitted by arthropods (lice, fleas, ticks and mites). These zoonoses are among the oldest known vector borne diseases. In Europe, only *Rickettsia* spp. are etiological agents of rickettsioses [1].

There are several classifications of *Rickettsia* spp. The most widely used is one that divides this genus into spotted fever group (SFG) and typhus group (TG). Other classifications distinguish also an ancestral group and a transitional group. In this mini-review, we will describe rickettsioses according to the vector.

2. Louse-borne rickettsiosis

Epidemic typhus or louse-borne rickettsiosis is caused by *Rickettsia prowazekii* and transmitted by the body louse, *Pediculus humanus corporis*. Nowadays this infection is not present in Europe, but some sporadic cases, imported ones and recrudescent forms have been described in this continent

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[2–4]. Although the risk of an epidemic is very low, an outbreak can occur as a result of the catastrophic breakdown of social conditions in which dirt and cold can lead to lice epidemic and lice can feed on a human with a recrudescent form of epidemic typhus (Brill-Zinsser disease). We should suspect *R. prowazekii* infection in people with unfavorable hygienic conditions presenting fever, headache and rash. Rash can be absent or very difficult to see, especially in dark skinned people. In these cases, the only way to suspect body lice infestation is to search signs of scratching of the skin. Body lice are not found on the body but are found in the seams and clothing [5].

3. Flea borne rickettsioses

There are at least three flea species that bite humans in Europe (*Xenopsylla cheopis*, *Ctenocephalides felis* and *Pulex irritans*), and two of them are able to transmit rickettsia.

3.1. Murine typhus or endemic typhus

Murine typhus or endemic typhus is one of the most widely distributed arthropod-borne infections. The causative agent is *Rickettsia typhi* and the main vector is the rat flea (*X. cheopis*). It can also be transmitted by the cat flea (*C. felis*). Rats (*Rattus norvegicus* and *Rattus rattus*) are the reservoirs. This infection is common in Mediterranean countries, with important series from Spain, Croatia, Greece and Cyprus [6–11], and imported or sporadic cases from all Europe [12–15]. The typical triad (fever, headache and rash) is present in about 70% cases. Murine typhus is often unrecognized and substantially under reported [16]. Severity of murine typhus infection has been associated to age, race and delay in diagnosis. In some series [9], the lung infiltrates were very common (up to 53.7%). Nowadays, in many areas where the hygienic conditions have improved, the cat flea might be the main vector.

3.2. Rickettsia felis *infection*

***R. felis* infection** is distributed worldwide, and mainly transmitted by the cat flea (*C. felis*). It is worth mentioning that cat flea bites are very common, and the prevalence of *R. felis* in vectors is very high throughout Europe. However, only ten cases have been published since the first report in Germany in 1997 [17–21]. In Europe the reservoir of this pathogenic bacterium is unknown. Apart from fleas, other vectors are being reported all over the world.

According to the data reported from Europe, *R. felis* infection was more frequent in male (70%) than female patients, and affected humans of all ages (from 12 to 89 years; average of 42.8 years) without a typical seasonal presentation. Fever and headache were the most reported clinical signs (60%). Rash was described in 40% cases and an eschar, in 10% patients. Neurological involvement was documented for all Swedish cases (subacute meningitis, Bell's palsy and deafness) [17–21].

4. Tick borne rickettsioses

Tick-borne rickettsioses (TBR) are the main source of *Rickettsia* infections in Europe. It was suspected that other etiological agents different from *Rickettsia conorii* subsp. *conorii* were causing TBR. However, only Mediterranean spotted fever (MSF) was diagnosed before the incorporation of molecular biology tools to the clinical practice. Nowadays, the microbiological spectrum of TBR is broad and it includes other *Rickettsia* spp. causing MSF-like pictures, such as *Rickettsia helvetica* and *Rickettsia monacensis* (transmitted by *Ixodes ricinus*), *Rickettsia massiliae* (transmitted by ticks belonging to the *Rhipicephalus sanguineus* complex) or *Rickettsia aeschlimannii* (transmitted by *Hyalomma* spp.). In the 1990's, similar cases that involved lymphangitis were described. Moreover, a syndrome transmitted by *Dermacentor* ticks has been also described. Necrosis, erythema and lymphadenopathy are the most prominent signs whereas systemic signs such as fever do not usually appear.

4.1. Mediterranean spotted fever (MSF) and MSF-like

4.1.1. Rickettsia conorii

R. conorii* subsp. *conorii is the main etiological agent of MSF in Europe, followed by ***R. conorii* subsp. *israelensis*** (this last one, mainly in Portugal). In addition, *R. conorii caspia* has been found in ticks removed from military personnel in Kosovo but no human cases have been reported [22]. Recently in Spain, ***R. conorii* subsp. *indica*** has been detected in blood specimens from two patients with MSF (personal communication, unpublished data). In Europe, this subspecies had been confirmed only in one patient from Sicily by PCR [23].

The involved vector of MSF is the brown dog tick *Rh. sanguineus* and probably, the related species. These ticks are not only the vectors but also the main reservoirs, since dogs can suffer the illness [24]. MSF has been described in nearly all Mediterranean countries with important series from France, Spain, Italy, Portugal, Greece, Croatia, Turkey, Switzerland, Romania and Bulgaria [25–30].

The incubation period of MSF usually lasts 7 days, and it is typical to find an eschar even in 90% cases. Multiple eschars can be observed, more frequently in children. Sudden fever appears in all cases and it is accompanied by chills, headache and myalgias. From 3 to 5 days after the onset of fever, a rash appears. It is a maculo-papular rash with purpuric elements in some cases that is more frequent in extremities and typically affects palms and soles. Fatal or complicated cases have been reported even in 32% cases, and they have been related to different subspecies, such as *R. conorii* subsp. *israelensis*, and associated to delayed diagnosis and treatment, wrong antimicrobial drug choice, elderly people, immunosuppression, chronic alcoholism, glucose-6-phosphate dehydrogenase deficiency, diabetes or smoking [25,31–34].

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4.1.2. Rickettsia helvetica

R. helvetica may also cause MSF-like. Cases from France, Switzerland, Italy and Sweden have been reported [25]. Interestingly, it has been involved in cases of sudden death associated to perimyocarditis and in cases of meningitis, all of them in Sweden [25]. The vector is *I. ricinus*.

4.1.3. Rickettsia monacensis

R. monacensis is another human pathogenic *Rickettsia* species. As its vector (*I. ricinus*), this *Rickettsia* sp. is distributed throughout Europe but only 4 cases have been reported: two cases (blood cultured) from the North of Spain [35], one case from Sardinia, Italy [36], and the remaining one, from Croatia [37]. All of them resembled MSF.

4.1.4. Rickettsia sibirica mongolitimonae

R. sibirica mongolitimonae is other *Rickettsia* spp. that can cause MSF-like illness. Since the description of the first human case in France in 1996, patients and series from France, Spain, Portugal and Greece have been documented [25,38–45]. Since lymphangitis was observed in patients affected by this rickettsia, the infection was named 'Lymphangitis Associated Rickettsiosis' (LAR). The involved vectors are at least *Hyalomma* spp. and *Rhipicephalus pusillus*.

To date, a total of 27 cases have been reported. The average age of the patients was 51.8 years (from 20 to 76 years) and the infection was more frequent in male than female patients. Cases were distributed throughout the year, more frequently in spring and summer. The main clinical characteristics were fever (27/27; 100%), eschar (23/27; 85%) and lymphangitis (10/27; 37%) [25,38–45].

4.1.5. Rickettsia massiliae

R. massiliae was recovered using PCR from a 20-year-frozen sample of a patient with a MSF-like illness in Sicily in 2006. Since then, human cases from France and one case from Spain acquired in Argentina have been reported [25,46]. It is feasible that some MSF cases are caused by *R. massiliae*. This *Rickettsia* sp. is associated to European ticks belonging to the *Rh. sanguineus* complex that frequently bite humans, and it has been usually found when searching throughout Europe.

4.1.6. Rickettsia aeschlimannii

R. aeschlimannii is other *Rickettsia* sp. broadly distributed by the Mediterranean area of Europe. Its prevalence in *Hyalomma marginatum*, which is the involved vector, is high [25]. Only one European case has been reported from Greece [47]. According to our data, the risk of developing a spotted fever rickettsiosis after having been bitten by *Hy. marginatum* infected with *R. aeschlimannii* was very low. We studied 43 patients of whom had these characteristics, and none of them developed either an infection or illness. On the other hand we have studied one patient who developed an erythema migrans-like lesion after having been bitten by *Hy. marginatum* but the tick was not found to be infected with *R. aeschlimannii* or *Borrelia burgdorferi* [48].

4.2. TIBOLA/DEBONEL/SENLAT

These are the acronyms of 'Tick-Borne Lymphadenopathy', '*Dermacentor*-Borne Necrosis Erythema Lymphadenopathy' and 'Scalp Eschar and Neck Lymphadenopathy After Tick Bite'. The involved agents are *Rickettsia slovaca*, *Candidatus* Rickettsia rioja and *Rickettsia raoultii*. The main vector is *Dermacentor marginatus* although *Dermacentor reticulatus* has also been involved. Clinical manifestations include an eschar at the site of the tick attachment (nearly always on the scalp) surrounded by an erythema and regional/painful lymphadenopathies. If the tick bite is on the scalp, patients may suffer from facial edema. If the tick bite is located outside of the scalp, an erythema (similar to the erythema migrans typical from Lyme disease) with an eschar at the site of the tick-bite usually appears. Since the first reported cases from Hungary, France and Spain, there are several series reported from these countries as well as from Portugal, and sporadic cases from other European countries [25], recently including United Kingdom [49].

5. Mite-borne rickettsiosis

5.1. Rickettsialpox

Rickettsia akari is the etiological agent of rickettsialpox. It is commonly transmitted by the bite of the house-mouse mite, *Liponyssoides sanguineus*, that infects the common mouse (*Mus musculus*). Apart from Oceania, this infection is distributed all over the world although only two manuscripts are available from Europe [50,51].

The presence of *R. monacensis* and *R. helvetica* has been recently published in chiggers collected from rodents in Slovakia [52].

6. Future

In the last 10 years, several *Candidatus* Rickettsia spp. have been described in Europe (Table 1). To date, their pathogenic role for humans has not been demonstrated, with the exception of *Ca*. R. rioja and *Ca*. R. tarasivechiae. Another concern is whether global warming will affect the distribution of vectors, and if this will increase the number of tick bites and other arthropods, thus increasing the possibility of a bigger number of cases of rickettsiosis.

Table 1
Candidatus Rickettsia species detected in Europe.

Candidatus Rickettsia sp.	Associated tick	Reference
Candidatus Rickettsia rioja	*Dermacentor marginatus*	[53]
Candidatus Rickettsia vini	*Ixodes arboricola* *Ixodes ricinus*	[54]
Candidatus Rickettsia barbariae	*Rhipicephalus turanicus*	[55]
Candidatus Rickettsia kotlanii	*Ixodes* spp.	[56]
Candidatus Rickettsia siciliensis	*Rhipicephalus turanicus*	[57]
Candidatus Rickettsia tarasevichae	*Ixodes persulcatus*	[58]

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