



Review

Tick-borne lymphadenopathy, an emerging disease

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ABSTRACT

Tick-borne lymphadenopathy (TIBOLA) is a spotted fever group disease characterized by an eschar and pronounced enlarged lymph nodes after a scalp tick bite. The goal of this synopsis is to review the TIBOLA literature published until May 2013: Forty-one articles (reporting 537 cases) were included. There was a predominance of cases in females and young people. Spain, France, and Hungary reported the majority of cases, and they were mainly reported in the colder seasons. The involved tick bite was frequently on the scalp. *Rickettsia slovaca* was the most frequent identified bacterium and *Dermacentor marginatus* the most frequently identified vector. The most prescribed antibiotic was doxycycline. TIBOLA has the potential to emerge outside Europe: improving knowledge of TIBOLA may promote early symptoms recognition and may allow early treatment.

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Introduction

Rickettsia are intracellular bacteria associated with eukaryotic hosts (like arthropods and humans). They are subdivided in the spotted fever group, the typhus group, the *R. bellii* group, and the *R. canadensis* group (Parola et al., 2013). Tick-borne lymphadenopathy (TIBOLA) is a spotted fever group disease characterized by an eschar (necrosis of dermis and epidermis) and pronounced enlarged lymph nodes after a scalp tick bite. Although the first case dates back to 1987 (Lakos, 1999), it was first described by Raoult et al. (1997). Due to its clinical features, Lakos (1997) called this infection TIBOLA. Later on, Oteo et al. (2000) described a similar syndrome and named it *Dermacentor*-borne necrosis erythema and lymphadenopathy (DEBONEL) given that the sonority of TIBOLA (similar to EBOLA) could frighten the society. More recently, Angelakis et al. (2010a,b) renamed this illness as scalp eschar and neck lymphadenopathy (SENLAT). The term TIBOLA was the first to be used and reflects the most important symptom (lymphadenopathy) and the transmission mode. SENLAT and DEBONEL evoke complex terms like the vector “*Dermacentor*” and “eschar”. For these reasons, in this review, we have adopted the term TIBOLA.

The first identified etiological agent was *R. slovaca* (Raoult et al., 1997; Cazorla et al., 2003). Nowadays, there are also other agents

implicated in TIBOLA. The already identified vectors are the *Dermacentor* ticks: *D. marginatus* (Raoult et al., 1997) and *D. reticulatus* (Raoult et al., 2002). Vector distribution influences TIBOLA epidemiology (Raoult et al., 2002; Parola et al., 2009): *D. marginatus* is most frequently found in Mediterranean areas of Europe and North Africa and *D. reticulatus* in colder areas of western Europe, central Europe, and in areas of the former Soviet Union (Fig. 1). These ticks are probably the reservoirs of *R. slovaca* and *R. raoultii*; the geographic distribution of the ticks and the bacteria overlap (Parola et al., 2009).

TIBOLA is mostly caused by agents that were previously not considered pathogenic. It is an emerging disease that is gaining more significance in Europe surpassing, in some regions, the Mediterranean spotted fever (Guerrero et al., 2006; Ibarra et al., 2006). The aim of this synopsis is to review the available data about this disease.

Methods

We searched the query “*Rickettsia Infections*”[Mesh] AND (*Tibola*[All Fields] OR *Debonel*[All Fields] OR *Rickettsia slovaca* OR *Rickettsia raoultii*) in PubMed®, Scopus®, and Web of Science® in May 2013. We obtained 114 articles, after exclusion of the duplicates. Reading the title and the abstract allowed the exclusion of 55 articles (i.e., 59 included articles). A secondary manual search of references cited in the included articles was performed to find the relevant ones. After reading the full-text articles, we included 41 articles (all the English, French, and Spanish full-text reports regarding TIBOLA were included). Finally, we collected

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Fig. 1. (A) *Dermacentor reticulatus* (left hand side: female; center: male; right hand side: distribution). (B) *Dermacentor marginatus* (left hand side: engorged female; center left: unengorged female; center right: male; right hand side: distribution; scale bar: 1 cm). *Dermacentor marginatus* is commonly found in Mediterranean areas of Europe and North Africa and *D. reticulatus* in colder areas of western Europe and in the former Soviet Union. From Parola et al. (2009), also at <http://wwwnc.cdc.gov/eid/article/15/7/08-1449.htm>.

the following items: localization (country), number of patients, gender, age, season, clinical features, laboratory features, bacteria, tick, and treatment.

Thirty-seven articles reporting TIBOLA cases were found. The articles reported 537 cases of TIBOLA. The publication by Oteo et al. (2004) is an extension of Oteo et al. (2000) and Oteo and Ibarra (2002), and the publication by Lakos (2002) is an extension of Lakos (1997) and Lakos (1999).

Gender and age distribution

The gender distribution was the following: 154 males, 274 females. In 109 cases, the involved gender was not mentioned. Age was reported in different ways (ranges, averages, and medians) making its correct description impossible. Nevertheless, there was a tendency of TIBOLA to occur in young people. Several articles reported TIBOLA in children (Lakos, 1999, 2002; Lakos and Raoult, 1999; Oteo et al., 2000, 2004; Oteo and Ibarra, 2002; Raoult et al., 2002; Nieto et al., 2004; Ibarra et al., 2006; Minagorre et al., 2006; Lipsker et al., 2008; Porta et al., 2008; Selmi et al., 2008; Clopés et al., 2009; Parola et al., 2009; Angelakis et al., 2010a,b; Edouard et al., 2011; Gaston et al., 2011), and only 2 reports included people older than 65 years (Cazorla et al., 2003; Rieg et al., 2011). All the average and median ages reported were below 40 years.

TIBOLA has a high predominance in women and children, and the scalp is the most common area of tick biting (occasionally other hairy zones like axillae, thorax, or arms are involved). A possible explanation is that *Dermacentor* ticks are attracted to the often longer hair of women and girls (the hair could be like a shelter for them) (Raoult et al., 2002; Lipsker et al., 2008; Parola et al., 2009; Lakos et al., 2012). In fact, they are used to parasitize long-haired animals like horses and wild boar (Oteo et al., 2000; Lakos et al., 2012). The height of the vegetation where adult *Dermacentor* quest is similar to childrens' size, 1–1.5 m (Mechai et al.,

2009). This could explain why children are more exposed to these ticks.

Seasonality and geographic occurrence

The disease occurred more frequently in the colder seasons, i.e. autumn (41 cases), winter (43 cases), and spring (54 cases). There was one anecdotic report of 4 summer cases (Porta et al., 2008). It can be explained by the main seasonal period of vector activity, as *D. marginatus* is most active from early autumn to winter (Ibarra et al., 2006). However, we noticed that spring is also a high incidence season. By contrast, Mediterranean spotted fever and Lyme borreliosis (other tick-borne diseases) occur most often during summer (Oteo et al., 2003).

The great majority of cases were from Spain (218 cases) (Oteo et al., 2000, 2003, 2004; Nieto et al., 2004; Bartolome et al., 2005; Ibarra et al., 2005a, 2005b, 2006; Guerrero et al., 2006; Minagorre et al., 2006; Porta et al., 2008; Allegue et al., 2009; Clopés et al., 2009; Perez-Perez et al., 2010). Other European countries such as Hungary (164 cases) (Lakos, 1997, 1999, 2002; Lakos and Raoult, 1999; Raoult et al., 2002; Lakos et al., 2012; Földvári et al., 2013) and France (146 cases) (Raoult et al., 1997, 2002; Cazorla et al., 2003; Rolain et al., 2005; Gouriet et al., 2006; Lipsker et al., 2008; Mechai et al., 2009; Parola et al., 2009; Angelakis et al., 2010a,b; Edouard et al., 2011; Gaston et al., 2011) had also numerous reports. There were only few reported cases in Italy (Selmi et al., 2008), Germany (Pluta et al., 2009; Rieg et al., 2011), Bulgaria (Komitova et al., 2003), and Poland (Switaj et al., 2012).

This can be explained by a publication bias: it was in these countries that TIBOLA began to be described, and probably the medical professionals have a lower suspicion threshold for this diagnosis. There are still no reports from outside Europe; cases of TIBOLA can potentially occur, for example, in North Africa where both *R. slovaca* and *D. marginatus* have already been identified (Cazorla et al., 2008; Parola et al., 2009, 2013).

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