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Tick-borne lymphadenopathy (TIBOLA)

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Summary. *Introduction:* From 1996 through 2000, we collected data on 86 patients with similar symptoms following a tick bite. The inclusion criteria were: enlarged regional lymph nodes and/or vesicular-ulcerative local reaction at the site of the tick bite.

Methods: Epidemiological and clinical data on these 86 patients were statistically analysed. All patients were tested for borrelia and 73 cases for *Rickettsia slovaca* antibodies by immunoblot. Fine-needle lymph node and/or skin biopsy was done in 13 patients. Genomic PCR amplification was performed on these biopsy samples.

Results: Seventy-six patients described an "extremely big" tick, and/or recognised a *Dermacentor* spp. tick from a collection of several species indigenous to Hungary. The tick bite was usually (96%) located on the scalp region. The time from the recognition of the tick bite to the first symptom varied between 0 and 55 (mean nine) days. A characteristic local reaction (eschar) was seen in 70 (82%) patients. The eschar can be surrounded by a circular erythema (18 cases, 21%). The other main symptoms are the enlarged and sometimes painful lymph nodes in the region of the tick bite, characteristically in the occipital region and/or behind the sternocleidomastoideal muscle. The most frequent general symptoms were low-grade fever, fatigue, dizziness, headache, sweat, myalgia, arthralgia, and loss of appetite. Without treatment, the symptoms were seen to persist for as long as 18 months. One of the patients reported symptoms suggestive of encephalitis.

The infection occurs most commonly in young children (age range: 2–57 years, mean: 12.6 years, 63% less than 10 years of age). A female predominance was registered (50/36). Doxycycline treatment can shorten the usually benign illness.

R. slovaca PCR gave positive results from skin or lymph node biopsy samples in 10/13 (77%) patients.

Conclusion: We have described a new and frequent tick-borne infection, most probably caused by *R. slovaca.*

Key words: Tick-borne infection, *Rickettsia slovaca*, lymphadenopathy, *Dermacentor marginatus*, TIBOLA.

Introduction

Shortly after the first description of Lyme borreliosis in Hungary [1], the Centre for Tick-borne Diseases was opened and was visited by thousands of patients each year. In 1987, a patient was seen who had an unusual discharge from a local crustaceous skin reaction following a tick bite. The reaction was clearly distinct from the cutaneous reaction of Lyme disease. The local reaction and the enlarged lymph nodes surrounding it were thought to be the consequence of a secondary bacterial infection. Since the presentation of this case, additional very similar cases have been seen. In 1996, we began to collect serum specimens from similar cases with characteristic local reaction and lymphadenopathy in order to investigate the aetiology. The syndrome was named **ti**ck-**bo**rne **l**ymph**a**denopathy (TIBOLA) because of the most pronounced sign of enlarged lymph nodes [2]. In 1997, a case report of *Rickettsia slovaca* from France [3] included a description of the local skin reaction to a tick bite that was indistinguishable from those seen in Hungary.

Patients, materials and methods

Patients' inclusion criteria were: (a) a crustaceous and/or ulcerating local reaction after a tick bite and/or (b) apparent regional lymphadenopathy connected to a crustaceous and/or ulcerating local reaction and/or the tick bite. Eighty-six clinically very similar (TIBOLA) cases had been collected during the period March 1996-December 2000. The age range was 2–57 years, mean 12.6 (SD: 12.0), and the male/female ratio was 36/50. All patients were tested for *Borrelia burgdorferi* and 73 cases for *R. slovaca* antibodies by immunoblot. Fifty-five tick-bitten controls, matched for age, sex and date of tick bite, were selected from patients visiting the Centre for Tick-borne Diseases during the study period and were also tested for *R. slovaca* antibodies by immunoblot. Sixty serum specimens from 25 patients with TIBOLA were tested for antibodies to *Rickettsia conorii, R. siberica, R. helvetica, Bartonella henselae, B. quintana and for Francisella tularensis as well as for HGE agent* by indirect immunofluorescence. Fine-needle lymph node and/or skin biopsy was done in 13 patients. Genomic PCR amplification from these biopsy samples was performed in Marseilles.

During the second half of the study, patients or their parents were asked to choose from a collection of different ticks the most similar tick to the one that had been removed from the patient. The collection included partly or fully engorged larvae, nymphs, male and female ticks of *Ixodes* and *Dermacentor* species.

For statistical evaluation, 1269 Lyme patients with erythema migrans who visited the Centre for Tick-borne Diseases during the study period were used as controls. Their age range

was 0–88 years, mean 35.3 (SD: 20.5) years and the male to female ratio was 581/688. Statistical analysis was performed by computer program EPINFO version 6.04. Cross tabulation, Chi^2 and ANOVA were computed.

Results

Seventy-six (88%) patients recalled an extremely big tick or recognised a *Dermacentor* spp. tick from a collection of different tick species. Two ticks were preserved and taxonomically described as *Dermacentor marginatus*.

Sixty-two patients gave information on the geographical area where the tick was acquired. Most of the patients had been bitten in three regions of Hungary (Fig. 1). The seasonal distribution of tick bites associated with TIBOLA patients differed from that of Lyme patients. The monthly distribution of tick bites in TIBOLA and Lyme patients differed significantly ($p < 0.001$, $chi^2 = 42.4$, $d.f = 10$, Fig. 2). TIBOLA occurred more frequently during the colder months of the year. The average age of TIBOLA patients was 12.6 years (range 2–57) and was significantly younger ($p < 0.001$, $chi^2 = 56.7$, $d.f = 8$) than the average age (35.3 years) of Lyme patients (Fig. 3). There were more female patients than males in both the TIBOLA group (male/female ratio: 0.72) and the Lyme borreliosis group (M/F ratio: 0.84) but the ratios were not statistically significantly different ($p > 0.1$, $chi^2 = 0.47$).

The great majority, i.e. 83 (96.5%), of patients' tick bites and/or local reactions occurred on the scalp. One patient of three exceptions was bitten on the leg and two others on the trunk.

The first symptoms appeared at mean 9.0 days (range 1–55 days, SD: 9.9) after recognition of the tick bite. The presenting symptom was often a prominent and painful lymphadenopathy in the region of the tick bite**.** Because of the location of the tick bite in the majority of cases, the enlarged lymph nodes were usually located in the occipital scalp region and/or behind the sternocleidomastoideal muscle. Enlarged lymph nodes were registered in 71 (82.5%) patients. The mean number of palpable lymph nodes was 5.5 but varied between 1 and 20. Usually, one to three big lymph nodes with a diameter of 1–5 cm (0.4–2 inches) were found, together with smaller lymph nodes (Fig. 4). In one patient, a painful occipital tumor lasting for as long as 6 months was misdiagnosed as exostosis but disappeared after doxycycline treatment. Pain in the neck was a frequent complaint, especially during movements of the head.

The characteristic skin lesion (eschar) at the site of the tick bite was seen in 70 (81%) patients, and was the first symptom in 33 (38%) cases (Fig. 5). This local reaction started as a necrotizing papula or a vesicle, and was sometimes the centre of a swollen, inflamed area of 3–5 cm. A few days later, a yellowish, honey-like discharge was seen in 13 (15%) patients. In three patients, a haemangioma-like eruption developed at the site of the tick bite (Fig. 6).

Only 36 patients measured their temperature, the other 50 did not record fever. Eleven patients had low-grade fever (37–38 °C) and 13 had high fever (38–39 °C). The fever was usually short term (lasting for one or two days) and diminished in a week in every untreated case. Nearly half of the patients (41/86) mentioned myalgia, arthralgia, sweat or headache. Weeks or months after healing of the

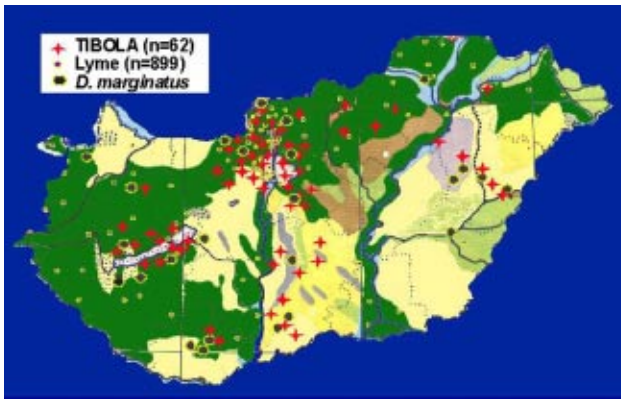

Fig. 1. Geographical distribution of TIBOLA patients. Only those patients who knew the exact region of acquiring the tick bite are presented here. For comparison, the distribution of Lyme patients visiting our Centre during the study period is also shown. *Dermacentor* infestation as described by Janisch [5] is also presented

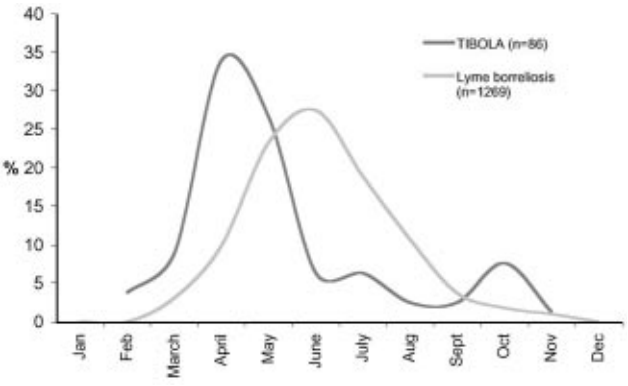

Fig. 2. Seasonal distribution of tick bite causing TIBOLA and Lyme borreliosis based on patients visiting the Centre for Tick-borne Diseases who knew the exact date of acquiring the tick bite

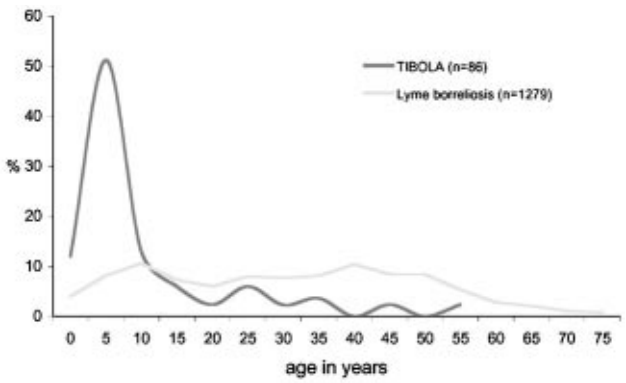

Fig. 3. Comparison of the age distribuiton of TIBOLA and Lyme patients

Fig. 4. TIBOLA patients with lymphadenopathy. Most of the enlarged lymph nodes are covered by hair. These photos represent only those patients whose lymph nodes are localised in the neck. Lymphadenopathy can be single but sometimes forms packets (see the right upper corner and the photo in the centre). Lymphadenopathy is sometimes visible together with the developing eschar (left lower corner and in the centre of the lower row)

eschar, a local alopecia 1–5 cm in diameter developed in 30/76 (39.5%) patients who were followed up (Fig. 7). This alopecia lasted months or years.

Laboratory results

Three patients had elevated erythrocyte sedimentation rates (30, 55 and 78 mm/h), three more had increased white-cell counts (9.1, 12.0 and 12.1), and two patients had mild leucopenia (WBC 4.1 and 4.6 /L). Two patients showed monocytosis (10% and 17% of leucocytes). One patient had elevated GOT (100 IU/L), GPT (48 IU/L), and GammaGT (367 IU/L) levels**,** and presented on physical examination a mild hepatomegaly, which disappeared after two weeks. *Staphylococcus aureus* was cultured from the discharges of the eruption in two out of seven cultures taken. No fungi were isolated or microscopically confirmed, when examined in three cases.

Of the 73 patients tested, 19 (26%) were positive by *R. slovaca* immunoblot. Two patients showed an IgM reaction only, three were positive for both IgM and IgG, the remaining 14 had only IgG antibodies. Only 2/55 (4%) age and sex-matched controls had a positive reaction in IgG testing and none in IgM. Both of the serologically positive controls had had more than 40 tick bites in the previous years. None of the patients tested had a positive or higher titre for rickettsiae other than *R. slovaca* in cross-absorption tests. None of them was positive for bartonellae, tularaemia, or for HGE agent in indirect immunofluorescence tests.

Lyme borreliosis serology (immunoblot) was positive in 8 (9%) patients. One of the Lyme serologically positive patients had had a typical erythema migrans (EM) in the year before his TIBOLA. Two others had typical EM in a different region from the eschar. Both had IgM reactions in borrelia serology. Two other patients, who had no sign of Lyme borreliosis but were borrelia positive at the first visit, showed serological progression in borrelia immunoblot during the follow up. They were not treated until the borrelia seroprogression was detected. Otherwise, no association between Lyme seropositivity and the development of erythema surrounding the eschar was found. IFA serological testing for EBV and CMV in six patients tested and the Weil-Felix reaction in 27 patients tested was negative.

Fig. 5. Development of the eschar from a small papula to the pealing of the crust

Ten of the 13 (77%) patients tested gave positive PCR results. Six out of the ten (60%) fine-needle lymph node biopsy specimens, 2/9 (22%) serum samples, 2/4 (50%) skin biopsy samples, and one of the two crusts (50%) removed from the eschar were positive by PCR. (Details of the PCR method and cross-absorption test results will be published in a separate paper.)

Effect of the antibiotic treatment

Our intention was to treat only those patients who showed progressive symptoms. Fourteen patients whose symptoms seemed to resolve spontaneously remained untreated. Twenty-five patients were treated with more than one antibiotic; one patient received seven courses of different antibiotics. The mean treatment time was 21 days (range 5–60 days). Initially, azithromycin seemed to shorten the disease duration, but in two of the azithromycin-treated cases, symptoms progressed during treatment. After this experience, amoxicillin + clavulanic acid was tested. Again, it seemed to shorten the duration in some cases, but the symptoms of two patients worsened in spite of the treatment. Doxycycline treatment was then applied in 16 further patients, resulting in an impressive improvement in 12 of them. Two patients were treated with chloramphenicol and both showed resolution of symptoms by the end of the 5-day therapy (Table 1).

Discussion

The present study describes a new tick-transmitted infection with a homogeneous clinical presentation, typically consisting of a necrotic black eschar surrounded by a red halo on the site of a tick bite, which was most often in the occipital scalp. Moderately painful and chronic occipital or retro-sternocleidomastoideal lymphadenopathy is the hallmark of this disease, hence the proposed name "TIBOLA" or tick-borne lymphadenopathy. Recognition of the infection as a new entity was delayed by the perception that the local reaction and enlarged lymph nodes were consequences of a local secondary infection.

This theory of a pyogenous secondary infection was supported by the initial impression that some antibiotics seemed to shorten the disease, and by the cultivation of *Staphylococcus aureus* from the discharge in two cases. However, the protracted course with normal body temperature in a majority of cases, in sharp contrast to the persistence of frank and painful lymph nodes, argued against this idea. The long incubation period together with an often protracted remission period of the adenopathy, if no anti-

Table 1. Antibiotic treatment and resolution time of clinical symptoms

Antibiotic treatment	Number of patients	Resolution time (days – range)	Resolution time (days – mean)
None	14	12–180	62
Azithromycin or co-amoxiclav.	18	6–210	61
Doxycycline	16	10–138	50
Cloramphenicol	2	4–6	5
Multiple treatment	25		
Lost for follow up	11		

biotics were used as treatment, was also felt to be unusual. This coincidence of symptoms, very similar in every patient, suggested a new clinical entity presenting as a chronic but treatable tick-borne lymphadenopathy or TIBOLA.

The vector is probably *Dermacentor marginatus* (2–4]. This enormous tick seems to prefer hairy animals where it can safely hide. This may explain the reason why the tick bite is almost invariably found in the scalp region. The strong child predominance is likely to be due to the fact that children are bitten in the head region more frequently than adults are. The putative difference in tick vector may also explain the different seasonal distribution of cases when compared with infections transmitted by *Ixodes ricinus*. The geographical distribution of the reported location for the tick bite also corresponds to the area of *Dermacentor marginatus* infestation in Hungary [5]. There are only three *Dermacentor* sites where we have not yet registered TIBOLA patients.

The pathogenic role of an infection agent in TIBOLA is suggested by the long incubation period accompanied by a short-term fever in many cases, and the long-lasting local and generalized symptoms especially in the untreated patients.

A rickettsial aetiology was strongly suggested by the presence of an eschar and – in many cases – by the success of doxycycline and chloramphenicol treatment. A black eschar at the site of a tick bite is pathognomonic for the spotted fever group rickettsiae, and has not been described so far in other tick-transmitted diseases such as Lyme borreliosis, ehrlichiosis, and babesiosis. Scrub typhus, caused by *Orienta tsutsugamushi,* an agent related to *Rickettsia* and transmitted by larval trombiculid mites, can also be marked by an eschar. However, scrub typhus has only been described in the Far East, and is not characterised by lymphadenopathy. We have recently seen a patient who returned from South Africa with tick-bite fever, a

Fig. 6. Haemangioma-like eruption in TIBOLA

Fig. 7. Alopecia in TIBOLA. The photo in the right lower corner was taken two years after healing of TIBOLA

disease caused by *Rickettsia africae*. The eschar of this patient was equivalent to that regularly seen in TIBOLA.

Twenty-six per cent of the 73 patients tested showed a serological reaction in *R. slovaca* immunoblot, whereas only 2/55 age and sex-matched tick-bitten controls had a similar reaction. Both of the serologically positive controls had several tick bites before sampling. In a previous study, 98/472 (20.7%) *Dermacentor marginatus* ticks that were collected in two TIBOLA endemic regions harboured rickettsiae when examined by haemocyte test and Gimenez staining. In this study, 14/22 rickettsiae tested reacted with spotted fever group antibodies; six proved to be *Coxiella burnetii* [6]. This surprisingly high incidence of rickettsial organisms in the Hungarian *Dermacentor* fauna may explain why a serological reaction can be found in the tick-bitten population. As we used tick-bitten patients with different symptoms for testing the specificity our *R. slovaca* immunoblot, the 4% "false positivity" reflects a strong specificity.

Unfortunately, this serology was not sensitive. Only 26% of the patients tested gave a positive reaction. Our impression was that milder symptoms were more frequently accompanied by negative serological results, but we could not prove this statistically, perhaps because our database was not detailed enough for such a calculation. In mild infections that only have a limited duration, such as primary Lyme disease, the serological reaction is frequently weak. In previous years, PCR has proved to be a useful tool for the initial description of the etiologic agent of various rickettsioses due to *R. helvetica* [7] and *R. felis* [8], as in this study.

R. slovaca was discovered 30 years ago [4] but in spite of extensive investigations [9] its pathogenic potential remained an open question until recently [3]. The clinical picture described in the French index case [3], and previously also in a Czech patient [10], included CNS involvement, a manifestation that was also likely to have been present in one of our patients. However, in spite of the similarities, it is possible that the infection we describe is caused by a distinct subtype of *R. slovaca,* or by a related rickettsia.

Conclusion

TIBOLA can be defined as a characteristic local reaction at the site of a tick bite, usually located in the scalp region and surrounded by markedly enlarged and painful lymph nodes. The local reaction, developing days or weeks after the bite, starts as a papule or vesicle and develops to a crustaceous, necrotic and frequently secret-

ing lesion. The symptoms can persist for months or even years in untreated cases. The disease duration can be shortened by antibiotics, especially by doxycycline and perhaps chloramphenicol. Healing of the local reaction may leave a characteristic alopecia, which can be diagnostic months or even years after the tick bite. The striking uniformity of clinical symptoms suggests a common infectious agent in all cases. A spotted fever group rickettsia, most probably *R. slovaca* transmitted by *Dermacentor marginatus*, may be the etiologic agent. The vector and the agent causing the disease can be tentatively identified but remain to be confirmed by culture.

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