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Kontakt mit Pferden ist ein Riskofaktor für die Zecken-übertragene Lymphadenopathie (TIBOLA). Eine kontrollierte Fallstudie

Zusammenfassung Die durch Zecken übertragene Lymphadenopathie (TIBOLA) ist eine durch *Rickettsia slovaca* verursachte Infektion. Wir beschreiben in der vorliegenden Arbeit die saisonalen, Alters- und Geschlechts-mäßigen Charakteristika, sowie den Zusammenhang mit Kontakt mit Pferden als Risikofaktor für das Auftreten von TIBOLA im Vergleich zu einer anderen – häufigeren – Zeckenerkrankung, der Lyme Borreliose.

Wir analysierten Daten von 855 Patienten, bei denen entweder eine Lyme Borreliose ($n=805$) oder eine TIBOLA ($n=50$) diagnostiziert worden war, wobei wir Fischer's exakten Test oder generalisierte lineare Modelle verwendeten. Außerdem führten wir eine Alters- und Geschlechts-mäßig gematchte Fallkontrollstudie durch, bei der alle TIBOLA-Patienten mit einem im Alter und Geschlecht entsprechenden Patienten mit Lyme Borreliose verglichen wurden. Weiters identifizierten wir die Spezies der Zecken, die von den TIBOLA-Patienten gesammelt wurden ($n=16$).

Wir fanden, dass der Kontakt mit Pferden bei Patienten mit TIBOLA wesentlich häufiger (34/50; 68 %) als bei Patienten mit Lyme Borreliose war (110/805; 13,7 %) (OR = 13,35, $p<0{,}001$). Jüngeres Alter und weibliches Geschlecht waren mit einem höheren Risiko, TIBOLA zu bekommen, assoziiert (OR = 3,99, $p<0{,}001$). Zehn der 16 Zecken waren *D. marginatus*, 6 waren *D. reticulatus*, wodurch nahe gelegt wird, dass beide Spezies für die Übertragung von *R. slovaca* verantwortlich sind. Zwei Patienten wurden durch männliche Zecken infiziert. TIBOLA ist eine durch Zecken übertragene Krankheit (Zoonose), die einen spezifischen Zusammenhang mit Pferdekontakt haben könnte.

Schlüsselwörter: TIBOLA, Kontakt mit Pferden, Rickettsia slovaca, Zoonose, durch Zecken übertragene, Dermacentor-Zecken

Summary Tick-borne lymphadenopathy (TIBOLA) is an emerging infection caused by *Rickettsia slovaca*. We describe here the seasonal, age and gender characteristics as well as the association with horse contact as risk factors for acquiring TIBOLA in comparison with another, more frequent tick-borne disease, Lyme borreliosis.

We analysed a dataset of 855 patients diagnosed with either Lyme ($n=805$) or TIBOLA ($n=50$) disease using Fisher's exact tests and generalized linear models. Then we performed a matched case-control study in which all TIBOLA patients were paired with one Lyme patient matching in age and gender. We identified the species of ticks collected from the TIBOLA patients ($n=16$).

We found that horse contact was significantly more frequent among TIBOLA (34/50; 68 %) than among Lyme patients (110/805; 13.7 %) (OR = 13.35, $p<0.001$). The younger age and female gender associated with higher risk of acquiring TIBOLA (OR = 3.99, $p<0.001$). Ten of the 16 ticks were *D. marginatus*, six were *D. reticulatus* suggesting that both species are responsible for transmitting *R. slovaca*. Two patients acquired the infection from male ticks. TIBOLA is a tick-borne zoonosis, which might have a specific association with horse contact.

Keywords: TIBOLA, Horse contact, Rickettsia slovaca, Tick-borne zoonosis, Dermacentor ticks

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Introduction

The characteristic symptoms of tick-borne lymphadenopathy (TIBOLA) are an eschar in the scalp region with enlarged lymph node behind the sternocleidomastoidal muscle. These signs were first noted in 1987 and the syndrome, described in 27 patients, was named after the most pronounced clinical sign [1]. Publication of the new disease was strongly inspired by the first case report with microbiological confirmation of *Rickettsia slovaca* infection presented by Raoult et al. [2]. A Spanish group published details from a cohort of patients with the same symptoms under a different term: *Dermacentor*-borne necrosis and erythema with lymphadenopathy—DEBONEL [3]. Since then, some authors use the latter term for the same disease.

In 2002, we summarized the epidemiological and clinical data on 86 TIBOLA patients in Hungary [4]. In many cases, *R. slovaca* as a pathogen was proved by polymerase chain reaction tests on skin and lymph node biopsy samples and ticks [5]. *R. slovaca* is a spotted fever group *Rickettsia* and was first isolated in 1968 in Slovakia from *Dermacentor marginatus* ticks; it has also been detected in *D. reticulatus* in some parts of Europe [6]. Both species are commonly found on horses [7] and can also infest humans [6]. It has become apparent that most of our TIBOLA patients mentioned contact with horses at the time of tick bite. The aim of this study was to investigate whether contact with horses is an independent risk factor for TIBOLA compared to Lyme borreliosis.

Patients, materials and methods

Patients

Since 1987, a total of 202 TIBOLA patients have been diagnosed based on black eschar ("tache noir") at the site of the tick bite and enlarged (> 1 cm in diameter) lymph node(s) in the trapping region of the eschar. Diagnosis was performed at the Centre for Tick-borne Diseases, Budapest. Our centre is an outpatient service visited by 3,000 patients per year on average, located in the central part of Hungary accepting patients from the whole country since 1986. Patients are usually recommended by their doctors (family doctors, dermatologists, neurologists, paediatricians etc.) to attend the Centre, but patients are also accepted if they had recognized clinical signs or suspicions of tick-borne diseases by themselves. Between March 2007 and January 2010, we consecutively and prospectively asked our patients the following question: "Have you touched or met horses around that time when you got the tick bite, or if you have not recognized the tick, then have you met or touched horses in two months before your symptoms started?" Most of our patients mentioned direct contact, but we also considered indirect contact when horse was kept in the neighbourhood of a patient or when a patient visited a stable or walked on a horse-riding trail. All data were collected by a standard questionnaire. We consecutively and prospectively selected all patients who had typical symptoms for either Lyme borreliosis or TIBOLA. All patients were asked to come back for a follow-up visit 6 weeks after the first examination. Only those TIBOLA patients were treated by antibiotics who showed progressive clinical symptoms. Most of the TIBOLA patients healed spontaneously.

Serology

All but three TIBOLA patients' sera were tested by Vircell ELISA kit for *Rickettsia conorii* IgM and IgG antibodies. (Parents did not yield consent to cupping three children.) Serological progression and regression were arbitrarily defined if the difference between the extinction value of the acute and convalescent samples was at least 10 % of the strong positive control provided by the manufacturer. Sample pair (samples drawn from the same patient in different times) examinations were always run in parallel. The cut-off defined by the manufacturer corresponded with the 98 percentile of the 100 Hungarian healthy blood donors tested previously in our lab. All but three patients were tested for *Borrelia burgdorferi* sensu lato IgM and IgG antibodies by a homemade immunoblot based on ACA1 (*B. afzelii*) antigen. Sample pairs were always tested in parallel.

Ticks

In this study, we included only ticks removed from TIBOLA patients. Species identification was based on the morphological comparison of palps and coxae of the tick specimens under stereomicroscope as described in the identification keys [8, 9].

Geographical distribution

We registered the geographical locality of the tick bite. We used the partition of a road map, which divided Hungary into 89 grid boxes (Map of Hungary, Kartográfiai Vállalat 1991). The locality of the tick bite was registered by these grid boxes.

Data analysis

We explored the relationship between the relative risk of TIBOLA and the following explanatory variables: (i) age; (ii) gender (iii); locality of the tick bite; and (iv) the presence/absence of contact with horses. Firstly, an explorative analysis revealed that except locality, each explanatory variable had a significant effect on the relative risk of TIBOLA, therefore we included the three explanatory variables in a binomial generalized linear model (GLM) in which the incidence of TIBOLA was the response variable. GLM's can be viewed as an extension of linear regression models and can be used to model a wide range of distributions other than the normal distribution by linking the linear predictor to the response variable by a modified link function. These functions constrain the predicted values to be within a range of possible values—for incidence data, (using a logit link function), between 0 and 1 [10]. We applied a manual backward stepwise model selection, and *p*-value and Akaike's Information Criterion (AIC) value were used as criteria of acceptance [11].

To test the effect of contact with horses alone we had to exclude the possible confounding effects of age and gender, therefore we carried out a matched case-control study. As Lyme borreliosis cases greatly outnumbered the TIBOLA cases, we randomly selected one Lyme case to each case of TIBOLA matching in age and gender (using the "sample" function in R). We paid special attention to match any Lyme case to only one TIBOLA case. There were three TIBOLA cases to which the same Lyme case could be matched, so we omitted two cases of TIBOLA. We carried out this matching procedure for all TIBOLA cases 500 times and in each case we fitted a binomial model in which the only explanatory variable was the presence/absence of contact with horses.

Finally, we compared the seasonal distribution of dates when tick bites had been recognized on Lyme vs. TIBOLA patients using a Kolmogorov-Smirnov test. All analyses were performed using R 2.9.1 software [12], matched case-control study was carried out applying the package "survival" [13].

Results

We used a dataset of 855 patients diagnosed with either Lyme borreliosis ($n = 805$) or TIBOLA ($n = 50$). In all but two patients, the diagnosis was based exclusively on clinical signs: eschar plus regional lymphadenopathy for TIBOLA, or erythema migrans and/or Borrelia lymphocytoma for Lyme borreliosis. Two Lyme patients had peripheral facial palsy. The diagnosis was based on intrathecal Borrelia antibody production [14] in the latter cases. The occurrence of horse contact was 34 (68 %) of the 50 TIBOLA patients, while only 110 (13.7 %) of the 805 Lyme patients (Fisher's exact test odds ratio = 13.35, $p << 0.001$). Explorative analyses revealed that the relative risk of TIBOLA was significantly higher also for females (Fisher's exact test odds ratio = 3.99, $p << 0.001$) (Table 1). Distributions of patients' age were also significantly different for the two diseases (Fig. 1). People below the age of 20 years were at much higher risk to get TIBOLA than adults, while Lyme disease was equally frequent below 20 and between 30 and 60 years.

Table 1. Number of TIBOLA, Lyme cases and contact with horses for males and females

	Number of cases		Contact with horses	
	TIBOLA	Lyme	No	Yes
Males	9	376	332	53
Females	41	429	379	91

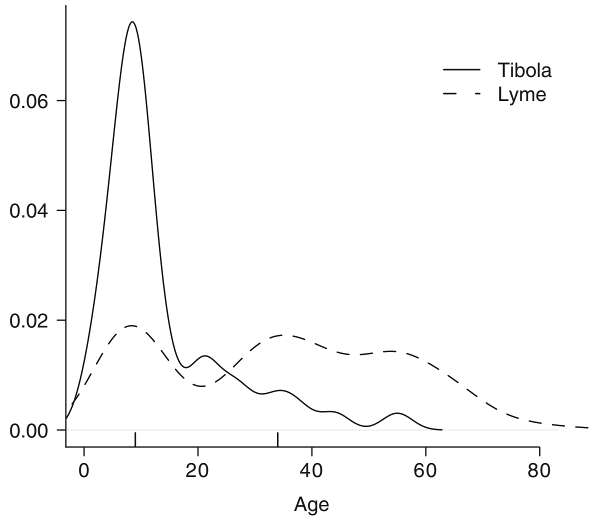

Fig. 1 Density plots of patients' age distributions for the two diseases. Rugs on the *x* axis indicate the medians of the two distributions (TIBOLA: 9 years, Lyme: 34 years). Kolmogorov-Smirnov test showed a significant difference between the two distributions (D = 0.519, $p << 0.001$)

In the best binomial GLM, three explanatory variables were significant (Table 2). The results indicated that risk of getting TIBOLA was 4.5 times higher for females, while the contact with horses increased the risk of TIBOLA by 9.5 times. One-year increase of age decreased the risk of TIBOLA by 6 %. However, we found significant correlations among the explanatory variables, as female patients were older ($F_{1,853} = 13.63$, $p << 0.001$) (female mean age = 34.86 years; male mean age = 29.55 years) and had contact with horses with a higher probability than males (Fisher's exact test OR = 0.665, $p = 0.035$). Patients having contact with horses were younger ($F_{1,853} = 26.62$, $p << 0.001$) (mean age without horse contact = 34.12 years; mean age with horse contact = 24.32 years). Due to this multicollinearity, the effects of the explanatory variables are confounded. From the 500 matching of TIBOLA cases with Lyme controls, fitting the binomial model was possible in 473 cases. The explanatory variable was highly significant in all cases with a mean effect of 2.43

Table 2. Results of the binomial GLM explaining the relative risk of TIBOLA. See text for detailed explanation

Explanatory variables	Parameters			Model		
	Estimation	Std. error	*p*-value	Deviance	df	AIC
Age	– 0.06	0.012	< 0.001	259.81	851	267.81
Gender: female	1.51	0.402	< 0.001			
Horse contact	2.25	0.338	< 0.001			

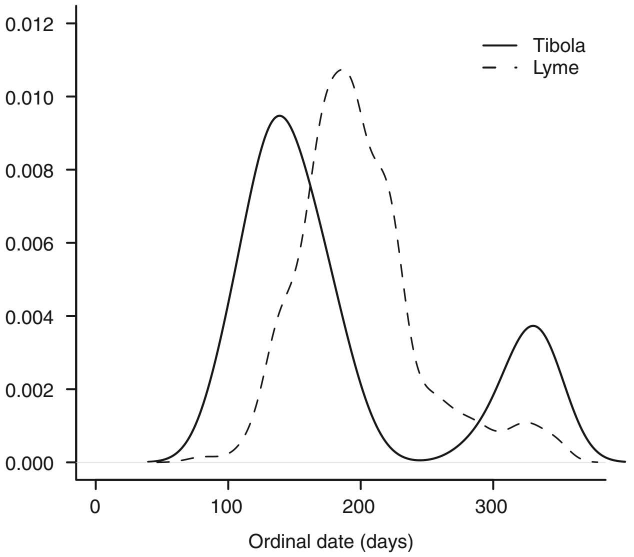

Fig. 2 Density plots of dates of tick-bites for the two diseases. Kolmogorov-Smirnov test showed a significant difference between the two distributions ($D=0.435$, $p<<0.001$)

indicating that patients having contact with horses are at ~11.3 times higher risk to get TIBOLA than patients without horse contact. Almost every patient of both groups mentioned direct or indirect contact with dog or cat but other animals were rarely registered.

We compared the seasonal distribution of dates when tick bites had been recognized on Lyme ($n=450$) vs. TIBOLA ($n=49$) patients. We found considerable differences in the seasonality of the two diseases (Fig. 2). TIBOLA showed a bimodal seasonality with a first peak in May and a second, smaller peak in November, while seasonal distribution of Lyme disease was unimodal with a peak in June. Furthermore, TIBOLA was almost absent in August. We did not find difference between TIBOLA and Lyme cases in the locality of acquiring the infection.

Ticks were available from 16 TIBOLA patients. All were adult, ten (nine females and one male) *D. marginatus*; the other six (five females and one male) were *D. reticulatus*. The collected *Dermacentor* ticks are currently being analysed for rickettsiae.

Four TIBOLA patients were positive for both IgG and IgM antibodies against *R. conorii*, ten for IgM and nine for IgG only. In eight of these 23 cases, we have seen serological conversion, and in 14 other cases the analysis revealed serological progression and/or regression during follow-up. In 24 cases (51 %) the test showed negative result but in all but three of these negatives follow-up samples were not available. We could not reveal any clinical difference between the serologically negative and positive patients.

Four TIBOLA patients revealed elevated *Borrelia* antibodies, two of them showed serological conversion. The clinical symptoms and course did not show difference in these latter cases of probable double infection.

Discussion

Our results provide clear evidence that apart from patients' age and gender, their contact with horses is an important risk factor for getting TIBOLA since more than two-third of the patients reported horse contact. Our dataset of 855 patients diagnosed with either Lyme borreliosis ($n=805$) or TIBOLA ($n=50$) supposedly constitutes a representative sample from the subgroup of the Hungarian population who is potentially at risk of tick-bite. Therefore, to reveal the risk factors for TIBOLA we used Lyme patients as a control group. We could avoid the patient selection bias in this way as the geographical location and knowledge of the centre influenced both patient groups equally.

The matched case-control analysis revealed that patients having contact with horses are at ~11 times higher risk of getting TIBOLA (instead of Lyme disease) than patients without horse contact. This corresponds to the results of the binomial model indicating that the effects of age, gender and contact with horses are hardly confounded. Although the interactions among these explanatory variables would be of particular interest, due to the small sample size for TIBOLA we could not test for these interactions. The risk for TIBOLA with horse contact was slightly lower in the matched case-control analysis than by the Fisher's exact test (11.3 vs 13.3), but both calculations represent a very strong relationship between horse contact and TIBOLA.

Although *D. marginatus* and *D. reticulatus* are known to infest horses [7, 15], a possible connection between contact with these animals and TIBOLA incidence has not previously been reported. We do not know whether horses are reservoirs for *R. slovaca* and it is also unknown whether *R. slovaca* can cause any symptom in horses. However, horses are definitely able to maintain large numbers of the adults of these two *Dermacentor* species [7, 15 and Földvári, G., unpublished results]. Thus, horses may effectively contribute to the maintenance of *R. slovaca* since they enable the survival of *Dermacentor* populations that have been suggested as reservoirs of these pathogens being able to transmit them both transstadially and transovarially. *Dermacentor* species are large ticks, a female *D. marginatus* measures up to 5.4 mm when unfed and 15 mm when fully engorged [8]. Adults of *D. marginatus* and *D. reticulatus* feed on wild and domesticated mammals and also humans. Janisch [15] described that in horses, most of the *Dermacentor* ticks had been found in mane and tail. This may explain the reason why the tick bite is almost invariably found in the scalp (hairy) region of humans. The longer hair that can provide a better shelter for these big ticks may also explain the female predominance. The strong child predominance is likely to be because children are bitten in the head more frequently (27 %) than adults (1 %) (Lakos, A. unpublished results). These factors (long hair and younger age with higher probability of the tick bite in head-neck region, tick bite during the colder months, as well as contact with horses) definitely increase the risk of acquiring TIBOLA. Our previous epidemiological analysis based on other patient groups resulted in very similar results concerning seasonality, age and sex distribution [4]. Similar seasonality, gender [16] and age distribution [17] was found by others but the importance of horse contact has only been observed in this study.

The colder and drier climate is better tolerated by the xerophilous *D. marginatus* and *D. reticulatus* species distributed in meadows [9] compared to *Ixodes ricinus* more commonly found in humid, wooded areas. A previous analysis of a larger group of TIBOLA ($n = 187$) patients showed that this infection is widely distributed in Hungary and the peak incidence compared to Lyme borreliosis is located between the two main rivers—Danube and Tisza [18]. This region is sparsely forested lowland with steppes, grassland and meadows characterized by relatively low humidity. The present study did not reveal similar statistical connection in locality of the infection, probably because of the smaller number of patients (data not shown).

Seasonality of TIBOLA is also shifted to the earlier and later months of the year compared to Lyme borreliosis [1, 4, 16], which again reflects to the differences in the life cycle and ecology of the vectors. Most of the TIBOLA patients have been registered in Hungary, France [4, 5] and Spain [17, 19], but we have diagnosed patients infected in Austria, Slovakia, Czech Republic, Romania, Slovenia and Italy. Case reports were presented also from Bulgaria, Italy and Germany [20–22]. The endemic area is probably spreading across the border of Hungary. However, publications are missing from the surrounding countries and we have not yet seen patients infected in Ukraine, Croatia or Serbia.

The clinical signs (eschar in the scalp and big lymph nodes in the occipital region as well as behind the sternocleidomastoidal muscles) are as characteristic for TIBOLA as erythema migrans for Lyme borreliosis, therefore serological confirmation is not necessary. The sensitivity of any type of *R. slovaca* serology is far from 100 % [5]. We have previously tried homemade indirect immunofluorescence tests and immunoblot (*R. slovaca* antigen was kindly provided by Didier Raoult). Commercial and homemade *R. slovaca* ELISAs were also tested but neither sensitivity nor specificity was appropriate (Lakos, A., unpublished results). Since cross-reaction between spotted fever group rickettsiae is intensive [5] we turned to *R. conorii* ELISA tests. In our hands, it provided a better sensitivity/specificity profile. In most of these presented patients who provided follow-up samples the *R. conorii* ELISA test showed clear serological evidence of spotted fever group *Rickettsia* infection. Although other spotted fever rickettsiae were identified in ticks [23, 24], we have no information on other human spotted fever group rickettsiosis in Hungary. *R. conorii* antibody testing seems to be an appropriate tool for supporting the diagnosis of TIBOLA in which the causative agent is not *R. conorii* but usually *R. slovaca*. We can exploit the cross-reactive capacity of *R. conorii* for supporting the diagnosis of TIBOLA as this test revealed highly specific based on the examination of Hungarian blood donors. As we previously observed, standard serological testing methods were insensitive especially when we applied it in the early phase of the disease. This may be explained by the fact that TIBOLA is a localized disease, unlike *R. conorii* infection. Testing the convalescence samples may improve the sensitivity of serology. DNA amplification by polymerase chain reaction was markedly more useful, especially when performed with a skin biopsy specimen or lymph node aspirate [5], but in this study we had not used this sampling for ethical reasons. Although the aim of this study was not to analyse diagnostic methods, our results were similar to our previous work confirming the usability of the present methods [5].

We are not aware of other reports with double infection (i.e. *B. burgdorferi* and *R. slovaca*). We did not find any discrepancy in the four, probably double-infected patients from the other TIBOLA patients.

Some ticks had been preserved by the Lyme patients which served as controls in the present study. All adults were *Ixodes ricinus* and none of them was *Dermacentor* not even in the group of the patients with horse contact. We did not register the exact number of these ticks collected from Lyme patients. Ticks (all but two females) were available from 16 TIBOLA patients. Ten were *D. marginatus*; the other six were identified as *D. reticulatus*. No difference was observed in clinical symptoms nor the course of the disease as a function of the tick species found. The relatively frequent occurrence of *D. reticulatus* is somewhat surprising, since most studies found only *D. marginatus* in TIBOLA patients [16, 19]. In an earlier French-Hungarian study, only three ticks were identified: two *D. marginatus* and one *D. reticulatus* [5]. Recent studies, which showed that, although to a lesser extent, *Rickettsia raoultii* and *R. rioja* can also cause TIBOLA, did not identify *D. reticulatus* on patients either [25, 26]. Our data suggest for the first time that *D. reticulatus* may be responsible to a similar extent for TIBOLA incidence as *D. marginatus*. We also showed first indirect evidence that both *D. marginatus* and *D. reticulatus* males are able to infect humans with *Rickettsia slovaca*. Feeding behaviour of male *Dermacentor* ticks can explain their possible role in pathogen transmission. Male *Dermacentor* ticks can feed on blood for 3–4 days compared to *Ixodes ricinus* males which generally feed only 6–8 h [27]. The ability of males to transmit disease agents has already been shown for some pathogens of veterinary interest [28]. We are analysing the *Dermacentor* specimens collected from our patients for the presence of *Rickettsia* spp. with molecular methods.

Conclusion

The highly significant association of horse contact with TIBOLA has not been reported previously. We cannot exclude that other factors than age, gender, seasonality and possibly geographical location may also contribute to the fact that TIBOLA patients reported significantly more frequently horse contact than Lyme patients. Among the above mentioned factors the horse contact seems to be the strongest risk factor for acquiring TIBOLA. Both *D. marginatus* and *D. reticulatus* are responsible for transmitting *R. slovaca*. We report for the first time the role of male *Dermacentor* ticks in TIBOLA infection.

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Authors' contributions

András Lakos M.D., Ph.D. designed the study, collected the information of the patients, performed the serological test for Lyme borreliosis and TIBOLA. He recognized the association between horse contact and acquiring TIBOLA. Ádám Kőrösi MSc, Ph.D. performed the statistical analyses. Gábor Földvári Msc, Ph.D. identified the tick species. All authors equally participated in the preparation of the manuscript.

Transparency declaration

Based on the review of the detailed description (objective, background, hypothesis, study design—collecting patients, their clinical and laboratory data, the number and age of the participant patients, the applied statistical methods, the time of study interval) as well as the wording of the informed consent the Expert Committee of the Hungarian Society for Infectious Diseases as a research ethics board supported the study entitled: Contact with horses is a risk factor for tick-borne lymphadenopathy (TIBOLA): A case control study. All patients provided a written informed consent: "I give my permission to Dr. Lakos to use the clinical and laboratory data collected on my (or my child's) illness for scientific analysis without mentioning my name and other personal information. This personal information must not be shared with other persons. I am aware that I have the right to withdraw my permission before the study will be closed." The study complied with the principles laid down in the Declaration of Helsinki.

Conflict of interest

The authors declare that they have no competing financial interests. They have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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