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CORRESPONDENCE

Published data do not support the notion that *Borrelia valaisiana* is human pathogenic

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Dear Sir or Madam,

We have noticed that in recent publications concerning the human pathogenicity of *Borrelia burgdorferi* sensu lato more and more often the genospecies *Borrelia valaisiana* is referred to as being human pathogenic. In this letter, we argue that the evidence for human pathogenicity of *B. valaisiana* is poor and only indirect and conspicuously contrasts the prevalence of this species in the European vector *Ixodes ricinus*. Therefore, in this letter, we make a case that this *Borrelia* genospecies is likely not human pathogenic for the reasons outlined below.

(1) The genospecies *B. valaisiana* was formally described in 1997 as a distinct genospecies of the *B. burgdorferi* sensu lato species complex being formerly referred to as *Borrelia* group VS116. It is clearly distinguishable by molecular means from other *B. burgdorferi* s.l. species, in particular from *B. garinii*, a genospecies that utilizes the same vertebrate hosts as reservoirs and is transmitted by the same tick vector, *I. ricinus*, as *B. valaisiana*. Several publications confirm that *B. valaisiana* strains have been isolated from ticks and propagated in culture just as it is the case for many other *Borrelia* species.

(2) The prevalence of *B. valaisiana* in questing *I. ricinus* ticks is comparable to other *Borrelia* species in Europe. To date, the most comprehensive meta-analysis on the prevalence of *Borrelia* genospecies in Europe is the review published by Rauter and Hartung [1]. Although it seems a bit dated, the trends published in this review hold still true to date and have been confirmed by many studies (too many to be included here) on the prevalence of *Borrelia* genospecies in various geographic regions of Europe.

The data presented in the above-mentioned review show clearly that in some areas in Europe, including the Czech Republic, France, Ireland and Slovakia, the prevalence of *B. valaisiana* is as high as or even higher than that of *B. garinii* [1].

This means that *B. valaisiana* is sufficiently frequent in the human-biting tick species *I. ricinus* that if it were human pathogenic it should be more frequently found in human patients. One would expect that at least one human isolate should have been obtained by now.

(3) *Borrelia valaisiana* is frequently reported in *I. ricinus* in Europe. This sharply contrasts the very limited numbers of reports relating *B. valaisiana* to human Lyme borreliosis. Furthermore, the evidence for *B. valaisiana* causing human Lyme borreliosis is only circumstantial as in the few reported cases ($n = 12$ in 20 years) where apparently *B. valaisiana* was found in humans only DNA evidence was provided [2–7]. To the best of our knowledge no single strain of *B. valaisiana* has yet been isolated from a human being. This is not because *B. valaisiana* is not cultivable; as mentioned above it has been cultivated many times from questing ticks.

In their report Rijpkema et al. [4] show that in two cases *B. valaisiana* DNA was amplified from skin rashes (erythema migrans) and detected in reverse line blots 2 and 4 weeks after detection of the rash. In two other cases, mixed infections of *B. garinii*, *B. afzelii* and *B. valaisiana* were recorded by PCR amplification and reverse line blot making it difficult to judge which of these was the symptom causing *Borrelia* species.

Schaarschmidt et al. [7] reported six cases of PCR amplification of *B. valaisiana* DNA from urine samples of

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humans (no *B. valaisiana* was detected in skin samples or CSF). There are several issues here that need to be mentioned. First, the authors report that there were no data on the clinical status of people providing the urine samples, so it was not possible to make any correlations between human symptoms/disease and *Borrelia* species for urine samples. According to the authors, there were mismatches in *B. valaisiana* sequences to the probes used in the study which may have caused misidentification and/or misinterpretation of the blots [7]. Last but not least, the method of urine analysis is controversial and not accepted for diagnostic purposes of Lyme borreliosis because of lack of specificity [6, 8].

In the study described by Godfroid et al. [3], only one of the serum samples showed a positive PCR for *B. valaisiana* but it was also PCR positive for *B. burgdorferi* sensu stricto, again making it difficult to decide which of the species caused symptoms.

Another report described amplification by PCR of *B. valaisiana* DNA from a resident of South Africa that visited on a regular basis the Greek island of Thassos [2]. Neither geographic region is known for sustaining natural transmission cycles of *B. burgdorferi* sensu lato. Furthermore, the patient was apparently treated intravenously with antibiotics from time to time. DNA extraction from CSF of this patient and PCR amplification of the flagellin gene resulted in a sequence that was closely related to *B. valaisiana* sequences. Although the symptoms of this patient may superficially support a diagnosis of Lyme neuroborreliosis, the most critical confirmative parameter to judge the case with certainty are missing from the publication, e.g. no CSF findings and no serological data were provided, data on therapy including outcome and follow-up CSF investigation are missing [8]. Thus, it is by no means clear that *B. valaisiana* was indeed the cause of the patient's symptoms.

A report from China found in one human sample DNA of a *B. valaisiana*-related genospecies [9]. However, phylogenetic sequence analysis of several loci revealed that the sample recovered from human tissue belonged to the rodent-adapted genospecies *B. yangtzensis,* not to *B. valaisiana* [9, 10].

Again, a different study from Japan reported PCR amplification and DNA sequencing of the flagellin gene from blood of 78-year-old man that had a tick attached to him [5]. DNA sequences revealed that the *Borrelia* flagellin sequence obtained from the man's blood had the highest identity (98.6%) to strain CKA1, a strain that was isolated from *Apodemus agrarius*, and most likely belongs to *B. yangtzensis* (again not *B. valaisiana*). The sequence showed only 96% similarity to *B. valaisiana* (strain VS116).

(4) Furthermore, a very different picture arises if one looks at truly human pathogenic *Borrelia* species such as *B. bavariensis*. This genospecies has been isolated frequently from human patients with typical symptoms of Lyme borreliosis (the strain collection of the German National reference Centre for *Borrelia* holds >25 human isolates of *B. bavariensis*) while it is rarely found in questing *I. ricinus*.

Thus, taken together, evidence that *B. valaisiana* is related to human Lyme borreliosis is very weak and only circumstantial as it is based on very few cases of DNA proof from human tissue samples. It is found in natural transmission cycles at a frequency that compares to, or even exceeds, that of other human pathogenic *Borrelia* species such as *B. garinii*, *B. afzelii* or *B. bavariensis*. It is vectored by the same ticks as other human pathogenic *Borrelia* species, thus ample opportunity should exist for this species to infect humans. Since its description in 1997, there are just two cases where DNA has been isolated from human skin with an erythema migrans lesion [4], all other cases either constitute different *Borrelia* species, are suspicious or relied on methods that are not accepted in diagnostics. We argue that these are compelling reasons to suggest that *B. valaisiana* is not human pathogenic.

Yours sincerely,

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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