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ORIGINAL COMMUNICATION

Prevalence and spectrum of residual symptoms in Lyme neuroborreliosis after pharmacological treatment: a systematic review

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Abstract Controversy exists about residual symptoms after pharmacological treatment of Lyme neuroborreliosis. Reports of disabling long-term sequels lead to concerns in patients and health care providers. We systematically reviewed the available evidence from studies reporting treatment of Lyme neuroborreliosis to assess the prevalence and spectrum of residual symptoms after treatment. A literature search was performed in three databases and three clinical trial registers to find eligible studies reporting on residual symptoms in patients after pharmacological treatment of LNB. Diagnosis must have been performed according to consensus-derived case definitions. No restrictions regarding study design or language were set. Symptom prevalence was pooled using a random-effects model. Forty-four eligible clinical trials and studies were found: 8 RCTs, 17 cohort studies, 2 case–control studies, and 17 case series. The follow-up period in the eligible studies ranged from 7 days to 20 years. The weighted mean proportion of residual symptoms was 28 % (95 % CI 23–34 %, $n = 34$ studies) for the latest reported time point. Prevalence of residual symptoms was statistically significantly higher in studies using the "possible" case definition ($p = 0.0048$). Cranial neuropathy, pain, paresis, cognitive disturbances, headache, and fatigue were statistically significantly lower in studies using the "probable/definite" case definition. LNB patients may experience residual symptoms after treatment with a prevalence of approximately 28 %. The prevalence and spectrum of residual symptoms differ according to the applied case definition. Symptoms like fatigue are not reported in studies using the "probable/definite" case definition. As the "possible" case definition is more unspecific, patients with other conditions may be included. Reports of debilitating fatigue and cognitive impairment after LNB, a "post-Lyme syndrome", could therefore be an artifact of unspecific case definitions in single studies.

Keywords Lyme disease · Lyme neuroborreliosis · Systematic review · Prevalence review · Residual symptoms · Fatigue

Introduction

Lyme neuroborreliosis (LNB) is a tick-borne infectious disease caused by the spirochete bacterium *Borrelia burgdorferi* sensu lato. Lyme disease is endemic in the temperate wooded regions of the Northern Hemisphere and has an incidence rate of about 111/100,000 per year [1]. Affection of the nervous system occurs in 3–15 % of all patients [1, 2]. Typical affections of the nervous system are polyradiculoneuritis (with or without cranial nerve affection) or meningitis. Affections of the central nervous system, such as encephalomyelitis, as well as borrelia-induced vasculitis with subsequent ischemic lesions may occur, especially in prolonged courses of the disease. In addition

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to nervous system affections, Lyme disease can affect other multiple organ systems like dermatological manifestations, arthritis, or, rarely, Lyme carditis [3]. Infection with the genospecies *Borrelia garinii*, which is common in Europe but not in North America, seems to affect the nervous system more often than other genospecies, such as *B. burgdorferi* sensu stricto or *Borrelia afzelii* [3]. LNB diagnosis is usually based on clinical presentation, serologic testing, and analysis of cerebrospinal fluid (CSF) [4]. There are tiered case definitions on the likelihood of diagnosis, depending on diagnostic results [5, 6]. Antibiotic treatment with beta-lactam antibiotics, like ceftriaxone, penicillin or cefotaxime, or doxycycline for 14–21 days is recommended by the guidelines of the European Federation of Neurological Sciences and the Infectious Diseases Society of America [4, 7]. Despite treatment, residual symptoms may persist, especially when late manifestations have occurred before the start of treatment, with considerable parenchymal damage, such as encephalomyelitis [6, 8]. Furthermore, the prevalence and spectrum of residual symptoms after treatment are subject to debate. Some authors postulate that a "post-treatment Lyme disease syndrome", consisting of debilitating fatigue and cognitive impairments, affects a considerable proportion of patients [9]. Some authors and patient support groups state that these patients suffer from chronic infection and should be treated with extensive antibiotic courses [10].

Interestingly enough, the repetition or extension of anti-infective treatment is not discussed for well-recognized residual symptoms, including pain, cognitive impairment, and fatigue, after the treatment of other infectious diseases of the nervous system, like viral encephalitis or post-herpetic radiculopathy [11, 12–13]. It therefore remains unclear how "post-treatment Lyme disease syndrome" can be validly diagnosed, what the actual symptoms are, and how common this syndrome is. Some authors argue that the cited symptoms are rather non-specific and that they exist as "background symptoms" in the general population, which is supported by case–control studies comparing patients with Lyme disease with healthy controls [14]. Other authors doubt the existence of this syndrome at all, stating that the patients described may actually have been suffering from other diseases, such as fibromyalgia, which eventually become unresponsive to antibiotic treatment [15].

This uncertainty and perceived severity of residual symptoms leads to anxiety and possible distrust in affected patients. Assessing the prevalence and spectrum of residual symptoms after treatment for LNB is therefore important for patient care because it can inform clinicians advising patients on what to expect after antibiotic treatment of LNB and provide information about what additional treatment may be required for residual symptoms. Knowing about the prevalence and spectrum of residual symptoms enables clinicians to provide mental support to patients who experience sequels after treatment. It is also valuable to assess which residual symptoms may be common after treatment and which are rather unusual, perhaps leading to doubt in the initial diagnosis and to additional diagnostic procedures for individual patients with unusual symptoms. To address this uncertainty, we performed a systematic review of the available evidence to assess the prevalence and spectrum of residual symptoms after pharmacological treatment of LNB.

Methods

Search

To assess the frequency and spectrum of residual symptoms in adult patients with Lyme neuroborreliosis after pharmacological treatment, we conducted a search for studies evaluating pharmacological treatments in this population. The treatment effects of different pharmacological options are also summarized elsewhere [16]. A comprehensive literature search was performed in three databases (Medline, EMBASE, and CENTRAL) and three clinical trial registers to source eligible studies and trials reporting on pharmacological treatment of LNB. The systematic review protocol, including the search strategy, was previously published [16].

Studies were eligible if they reported pharmacological treatment of adult patients with LNB. LNB diagnosis had to have been performed according to consensus-derived case definitions [6, 17]. Case series of less than five participants were excluded. No restrictions regarding study design or language were set.

The prevalence and spectrum of residual symptoms were extracted from the primary studies, as reported by the original authors. Whenever possible, we merged similar categories of symptoms for better comparability (e.g., "facial nerve palsy" was merged with "cranial nerve disorders"). Based on the information provided by the original authors, we assessed the single studies for the particular case definition used to diagnose LNB.

Weighted mean prevalence was calculated across all studies. There is no methodological consensus on how to summarize prevalence data. As considerable heterogeneity regarding interventions, length of treatment, follow-up, study design, and different case definitions was to be expected in the studies, we used a random-effects model to pool prevalence proportions as a primary analysis.

To assess the robustness of our analysis as well as small-study effects, we performed a sensitivity analysis using a fixed-effect model and provided the corresponding

estimates. Heterogeneity among studies was investigated with the I^2 test.

We conducted subgroup analyses for the prevalence and the spectrum of symptoms on the basis of the study design and case definition of LNB. As "probable" and "definite" case definitions are very similar, the prevalence rates in studies using these definitions were pooled for comparison with studies using the broader and perhaps more unspecific "possible" case definition. The spectrum of residual symptoms was provided as a proportion of single symptoms of all analyzed patients and as a proportion of single symptoms of all reported residual symptoms.

Publication bias for the prevalence of residual symptoms was investigated using a funnel plot, plotting the prevalence of single studies against the reciprocal value of the respective sample size. This method, however, was not validated for prevalence reviews. The funnel plot was visually inspected for asymmetry.

Comparisons between two datasets were performed with Pearson's χ^2 test with Yates' continuity correction [18]. Correlations were calculated using Pearson's correlation coefficient. A p value of <0.05 was regarded as statistically significant. Bonferroni's correction was applied when we were faced with multiple comparisons (e.g., for the spectrum of residual symptoms) [19]. Statistical analyses were conducted with R and Prism 4.0b for Macintosh [20, 21].

Results

The search identified 5779 bibliographic records after the removal of duplicates, of which 5660 were excluded and 118 full-text articles were retrieved for detailed examination. Forty-four studies met the eligibility criteria (Fig. 1; Appendix 1 for references): 8 RCTs, 17 cohort studies, 2 case–control studies, and 17 case series. Data on the prevalence of residual symptoms were extracted from 38 of these studies, and 31 provided data on the spectrum of residual symptoms. The studies were heterogeneous and considered applied interventions and length of follow-up (Appendix 2). Thirteen studies included patients according to the "probable/definite" case definition while 31 studies included patients according to the "possible" case definition. Details of the remaining symptoms varied across the primary study reports.

The quality of reporting varied considerably between studies. Some studies reported standardized follow-up periods for all patients, whereas others either had different follow-up periods for individual patients and reported the mean or median follow-up period or reported no information on the follow-up period. The follow-up period in the eligible studies ranged from 7 days to 20 years. Some studies provided detailed descriptions of the spectrum of

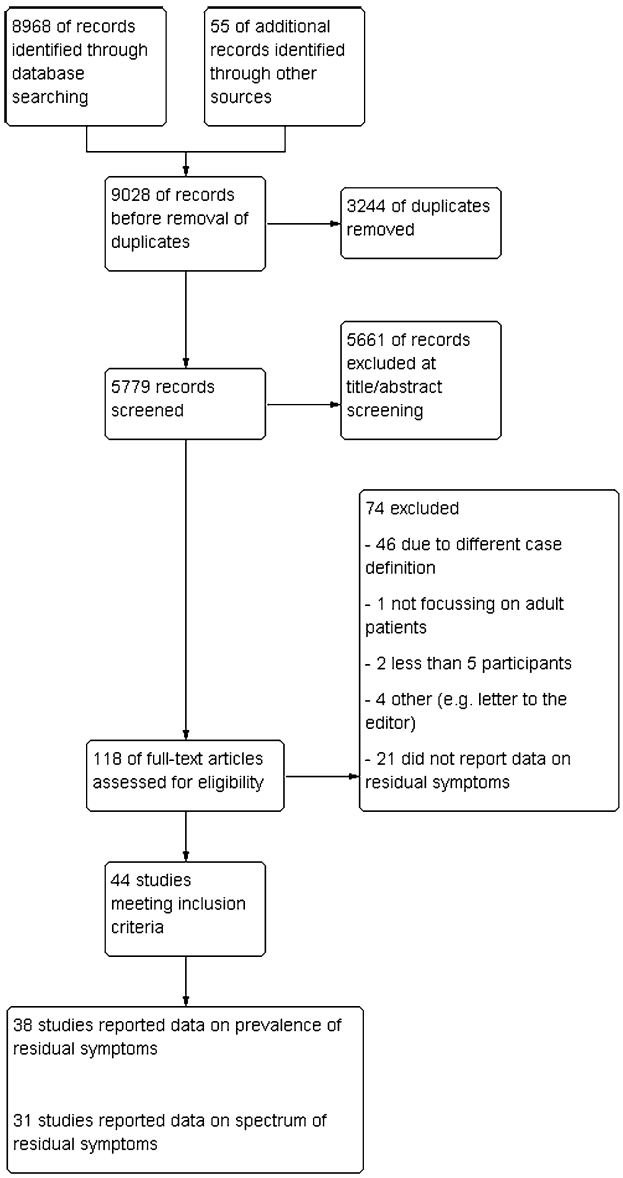

Fig. 1 Study flow diagram

residual symptoms, whereas others simply stated the proportion of patients with residual symptoms (Appendix 2). The severity of residual symptoms was assessed only in 7 studies, 6 of which described all residual symptoms as "mild" or "low grade", whereas 1 study differentiated between "minor" and "major" residual symptoms with considerable impact on daily life.

The prevalence of residual symptoms was reported for a total number of 547 patients in studies using the "probable/definite" case definition and for a total number of 922 patients in studies using the "possible" case definition. The prevalence of patients with residual symptoms varied considerably across studies. The mean weighted prevalence of any residual symptom in LNB patients at the last reported follow-up after pharmacological treatment in all

eligible studies irrespective of applied case definition was 28 % (95 % CI 23–34 %, $n = 34$, Fig. 2). Sensitivity analyses employing a fixed-effect model showed similar estimates (33 %, 95 % CI 30–35 %).

In the subgroup analyses, the mean weighted prevalence in studies only including patients meeting the case definition for "probable" or "definite" neuroborreliosis was 24 % (95 % CI 16–33 %, $n = 11$, Fig. 3). The mean weighted prevalence in studies only including patients meeting the case definition for "possible" neuroborreliosis was 31 % (95 % CI 25–37 %, $n = 27$, Fig. 4). Sensitivity analyses using a fixed-effect model showed similar estimates (28 %, 95 % CI 24–32 %) for the "probable/definite" case definition and 35 % (95 % CI 32–39 %) for the

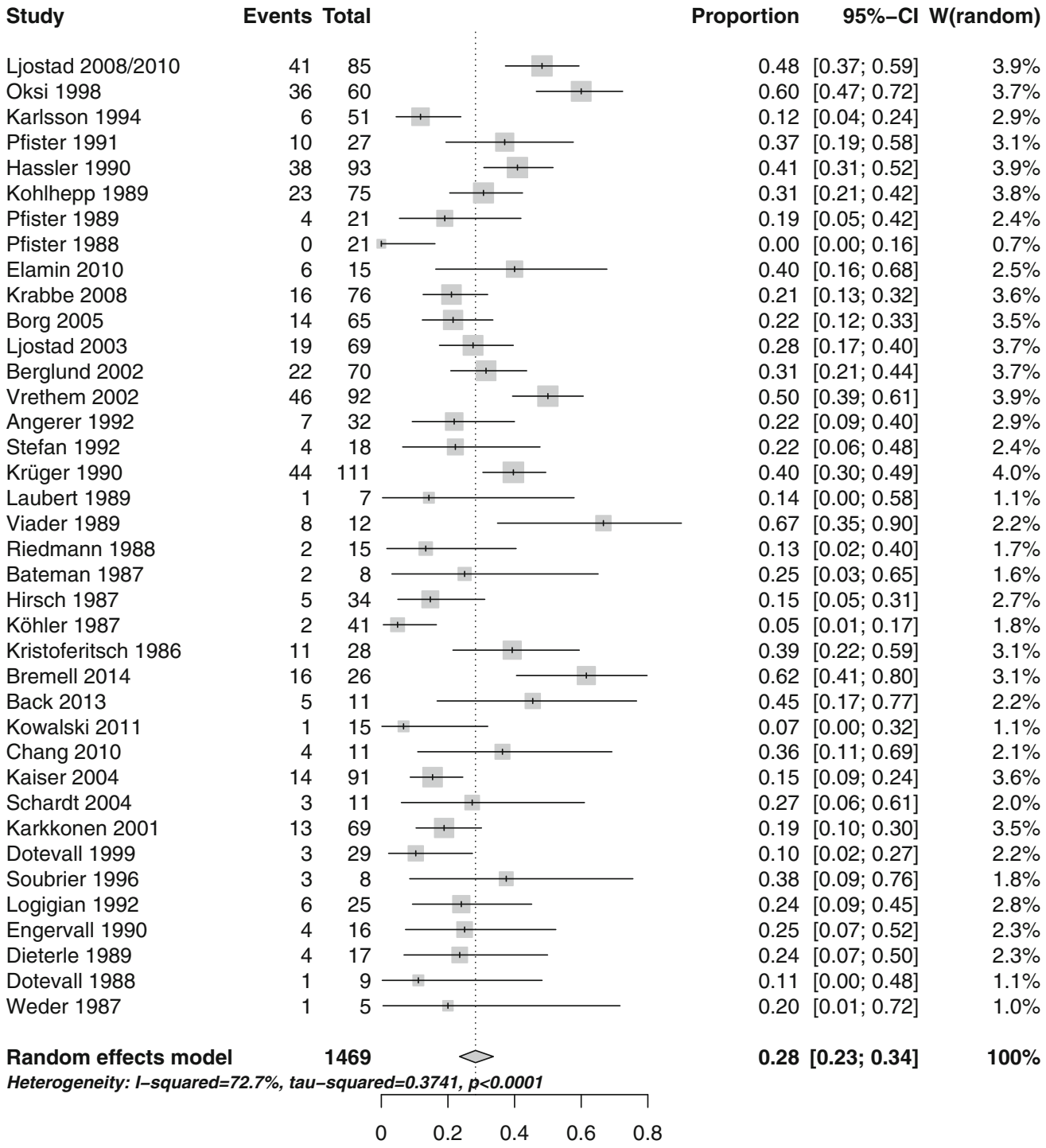

Fig. 2 Forest plot of prevalences of residual symptoms in all included studies

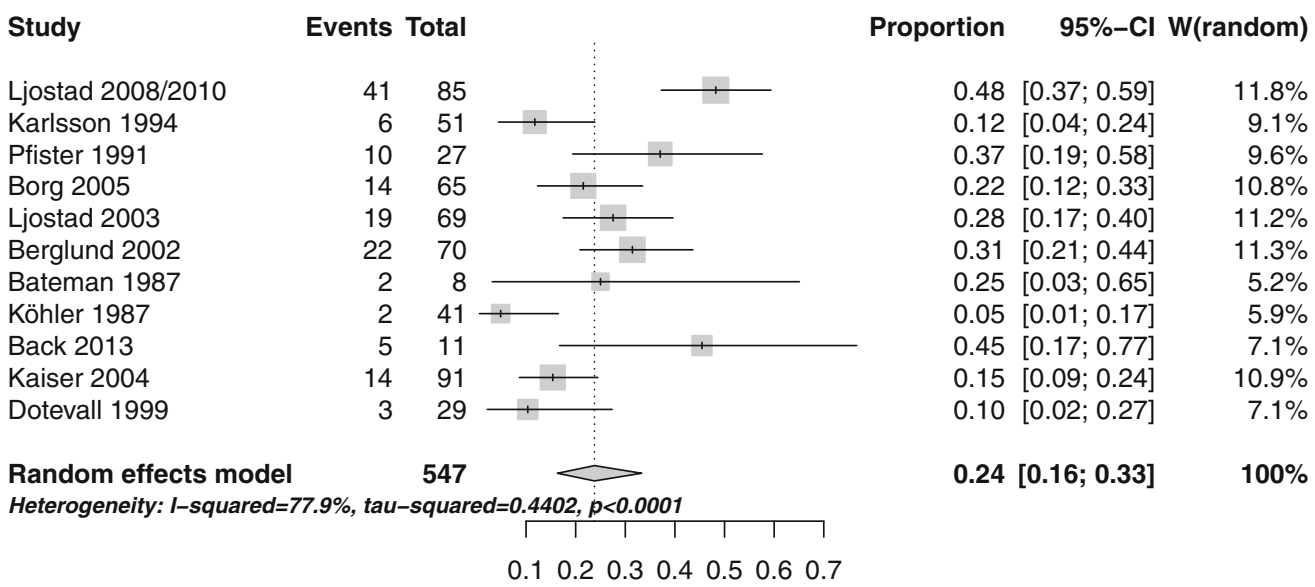

Fig. 3 Forest plot of prevalence of residual symptoms in eligible studies using the "probable/definite" case definition

"possible" case definition. The mean weighted prevalence of the residual symptoms was statistically significantly higher in studies using the "possible" case definition ($p = 0.0048$).

In other subgroup analyses, the mean weighted prevalence of residual symptoms according to the study design was 33 % in RCTs (95 % CI 23–46 %, $n = 8$), 28 % in cohort studies (95 % CI 22–36 %, $n = 16$), and 25 % in case series (95 % CI 18–34 %, $n = 14$). Sensitivity analyses using a fixed-effect model showed similar estimates for cohort studies and case series (32 %, 95 % CI 29–36 % and 24 %, 05 % CI 20–30 %, respectively), but a higher prevalence in RCTs (40 %, 95 % CI 35–45 %).

The mean weighted prevalence of residual symptoms was statistically significantly higher in RCTs than in case series ($p = 0.01885$), but not in relation to cohort studies ($p = 0.086$).

The year of publication of the primary studies did not correlate with reported prevalence levels (Pearson's $r = 0.3$, $p = 0.0638$). Publication bias and small-study effects were investigated in a funnel plot (Appendix 3), and our visual inspection identified no considerable publication bias.

The spectrum of residual symptoms was reported for a total of 687 patients in studies using the "probable/definite" case definition and for a total of 624 patients in studies using the "possible" case definition. As for the spectrum of residual symptoms, rarely reported symptoms were summarized as "diverse" (unspecific symptoms, encephalopathy, Parkinsonism, CNS involvement, hearing loss, impaired vision, micturition disorder, numbness, restless legs, and sleep difficulties). The most frequently reported symptoms in all eligible studies were pain, cranial neuropathy, cognitive impairment, and sensory disturbances (Table 1).

Patients with residual symptoms, such as cranial neuropathy, pain, paresis, cognitive disturbances, headache, fatigue, and diverse unspecific symptoms, were statistically significantly fewer in studies using the "probable/definite" case definition compared to the "possible" case definition (Table 1). In studies using the "probable/definite" case definition and reporting residual symptoms in detail, there were no reports of patients with residual fatigue.

Discussion

The mean prevalence of residual symptoms in studies of pharmacologically treated patients with LNB was approximately 28 %. Different LNB case definitions applied in single studies have different specificities. When the applied case definition was diffuse and unspecific, as in the case of the "possible" case definition, which often lacks verification of diagnosis via CSF analysis, the prevalence of residual symptoms was higher and the spectrum of residual symptoms was different compared to more strict case definitions, such as the "probable/definite" definition. Some symptoms, like fatigue, are not reported as residual symptoms in studies using the "probable/definite" case definition, and other symptoms, like cognitive disturbances, pain, and headache, were statistically significantly more common in studies using the "possible" case definition.

As the "possible" case definition is more unspecific, this difference could have arisen due to a higher number of "false positive" patients with conditions other than LNB included in these studies. Patients with other conditions falsely labeled

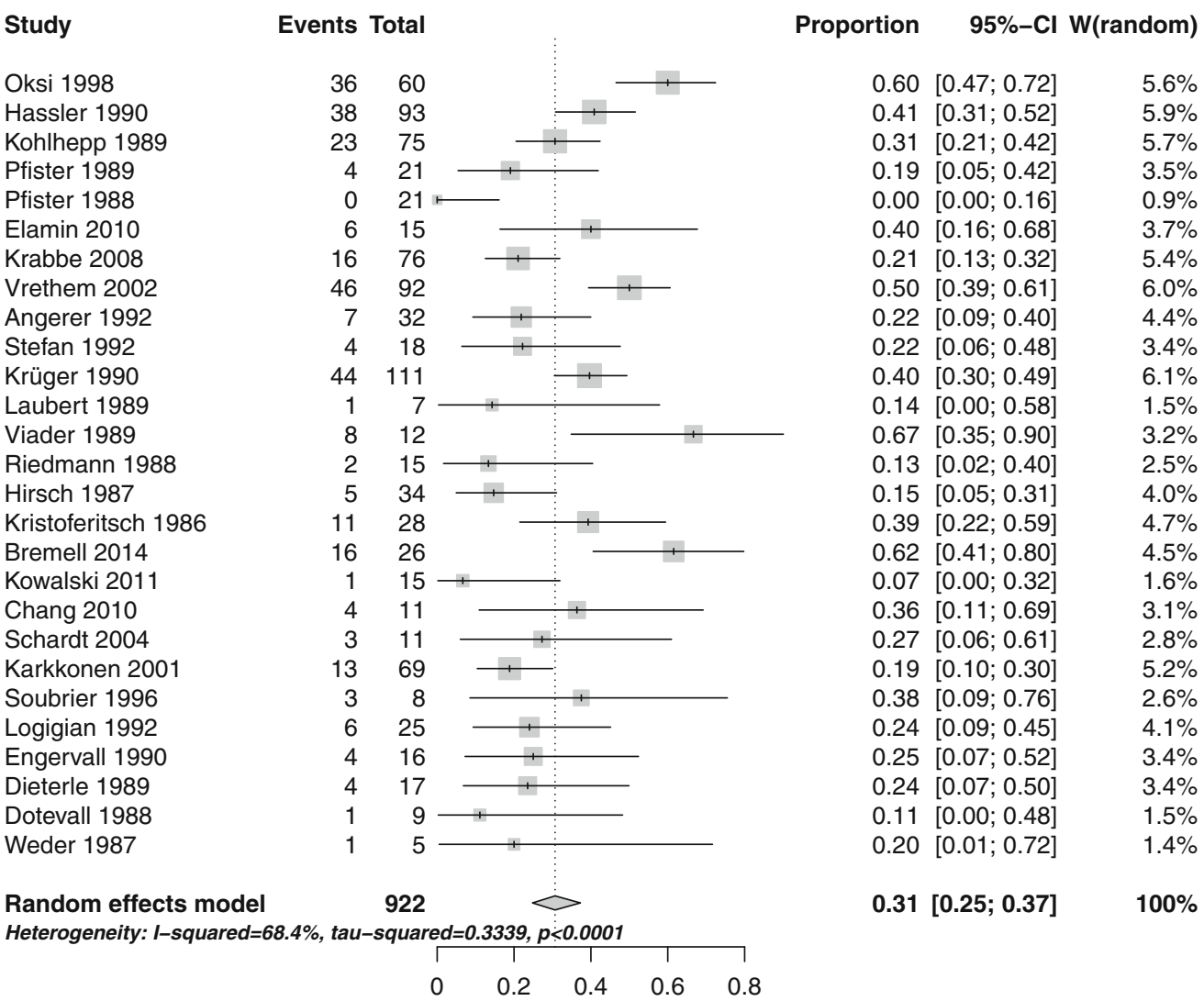

Fig. 4 Forest plot of prevalence of residual symptoms in eligible studies using the "possible" case definition

Table 1 Proportion of patients with residual symptoms (%) in eligible studies

Symptom	All studies (%) ($n = 1311$)	Probable/definite (%) ($n = 687$)	Possible (%) ($n = 624$)	p value
Cranial neuropathy	9.84	3.6	14.59	<0.0001*
Sensory disturbances	6.48	5.24	7.85	0.1483
Pain	10.37	2.77	18.75	<0.0001*
Paresis	5.57	2.33	9.13	<0.0001*
Unsteadiness/ataxia/vertigo	2.29	2.62	1.92	0.4329
Cognitive disturbances	8.77	1.6	16.67	<0.0001*
Headache	4.88	1.75	8.33	<0.0001*
Neurasthenia/fatigue	2.44	0	5.13	<0.0001*
Diverse	7.55	3.64	12.02	<0.0001*

Last column shows comparison of studies using different case definitions. * $p < 0.0055$ (level of significance adjusted via Bonferroni correction)

as Lyme neuroborreliosis may be unresponsive to antibiotic treatment and may therefore develop a different spectrum of residual symptoms after treatment. Reports of debilitating fatigue and cognitive impairment after LNB, a "post-Lyme syndrome", could therefore be an artifact of broad and unspecific case definitions in single studies, thus leading to inclusion of patients with other diseases.

Another explanation could be that patients accorded the "possible" case definition were at other "stages" of the disease than patients accorded the "probable/definite" definition. However, as the "possible" definition is broad and unspecific, this explanation is rather unlikely.

The prevalence of residual symptoms was higher in the eligible RCTs than in the case series. This could be due to a more standardized follow-up and assessment of individual patients in RCTs than in case series. Sensitivity analyses using a fixed-effect model showed a higher prevalence than was estimated from a random-effects model. As random-effects models place more weight on small studies, this could be explained by a higher prevalence of residual symptoms being more common in larger studies, thus revealing small-study effects in our analysis. As large studies were not exclusively RCTs, but also cohort studies, this difference cannot be explained by differences in methodological rigor alone. However, as the differences between the estimates from both models were small, this effect may be of marginal relevance.

We extracted the prevalence and spectrum of residual symptoms from studies reporting pharmacological treatment of Lyme neuroborreliosis. We did not include studies reporting on the natural course of the disease and may have missed those reporting only on the prevalence and spectrum of residual symptoms, without information on treatment, although it seems unlikely that authors would omit information on treatment when presenting residual symptoms after treatment. We focused on residual symptoms of Lyme neuroborreliosis, therefore our results may only be partly generalized on patients with other manifestations of Lyme disease. The follow-up period in the eligible studies was very heterogeneous and ranged from 7 days to 20 years. Subgroups investigating different follow-up periods were not possible due to limited reporting in primary studies. These heterogeneous follow-up periods may introduce bias in our findings, as studies with longer follow-up periods may report lower rates of residual symptoms.

Residual symptoms were not defined or uniformly reported. We merged similar categories of symptoms for better comparability, thereby possibly introducing bias by pooling slightly different symptoms across studies (e.g., "facial nerve palsy" and "abducens nerve palsy" were pooled as "cranial nerve disorders"). Another limitation of this review is that many of the selected studies were relatively old, coming from the 1990s or even 1980s. However, as the year of publication of the primary studies did not correlate with the reported prevalence of residual symptoms, the length of time since the studies were published may only have a limited effect on the estimates provided.

A strength of this review is the comprehensive literature search performed to gather all available evidence from studies evaluating pharmacological treatment for LNB patients. The risk of publication bias is difficult to assess in prevalence studies, but is likely low as a funnel plot of the prevalence of residual symptoms failed to show considerable asymmetry. The risk of spurious findings after multiple comparisons of single residual symptoms was minimized by applying the conservative Bonferroni correction. Heterogeneity was rather high in the pooled estimates. This could be partially explained from the observed differences between studies using different case definitions and study designs, although heterogeneity remained high in subgroups of different study designs or case definitions. Further, heterogeneity could have been derived from the different interventions and follow-up durations used in the primary studies. Differences in residual symptoms between studies could be related to the different agents used. However, assessing the efficacy of pharmacological treatments was not an objective of this study.

Although the prevalence and spectrum of residual symptoms could be extracted from the studies, it often remained unclear whether these symptoms had considerable impact on the quality of life of single patients. Interestingly enough, the long-term outcome of patients with LNB in terms of fatigue and quality of life was investigated in case–control studies comparing patients to healthy controls [22, 23–24]. The results remain inconclusive as some studies reported no statistically significant differences between patients and healthy controls while others found differences in single subscores of quality of life and fatigue. As case–control studies inherently suffer from sampling bias, the relevance of these findings remains unclear.

Narrative reviews state that the majority of patients treated for Lyme disease have excellent prognosis, with residual symptoms occurring in about 10–15 % of all patients [3, 25]. Our findings show that the prevalence of residual symptoms, as reported in the eligible studies, is considerably higher than expected. As a low prevalence of residual symptoms can be observed in patients with erythema migrans as a manifestation of early Lyme disease, more patients with LNB seem to develop residual symptoms according to the eligible evidence. This difference in the reported prevalence of residual symptoms has considerable impact on patient care as these patients may require additional treatments (e.g., analgesic agents for residual neuropathic pain or physiotherapy). However, as studies using the 'possible' case definition may have included considerable amounts of 'false positive' patients with

conditions ultimately unresponsive to antibiotic treatment, the pooled prevalence of residual symptoms may be overestimated.

The finding on the prevalence and spectrum of residual symptoms can be valuable for clinicians treating patients with Lyme neuroborreliosis, enabling them to give advice on what can be expected in terms of the prevalence and spectrum of residual symptoms after treatment. Knowing about the prevalence and spectrum of residual symptoms after treatment enables early initiation of additional therapies, such as analgesic agents, in corresponding patients. According to our data, some of the reported symptoms, like fatigue, are unusual for LNB. Clinicians faced with patients experiencing unusual symptoms (like fatigue) after antibiotic treatment may, based on this review, consider revising the initial diagnosis of Lyme neuroborreliosis, explore other diagnoses, and perhaps guide patients toward appropriate treatments.

Researchers planning future clinical trials on LNB should aim to apply the more specific "probable/definite" case definition as inclusion criteria for their studies as a way of minimizing the inclusion of "false positive" patients, thus increasing the possibility of obtaining unbiased results. When residual symptoms are reported, more emphasis should be placed on their impact on the quality of life so that their relevance for individual patients can be better assessed.

Compliance with ethical standards

Ethical standards The manuscript does not contain a primary clinical study or patient data.

Conflicts of interest SR reports receiving consulting and lecture fees, grant and research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Baxter, RG, and Teva. Furthermore, SR indicates that he is a founding executive board member of ravo Diagnostika GmbH. All other authors (RD, HS and JJM) declare that they have no competing interests.

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