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Signes fonctionnels chez les patients consultant pour une suspicion de borréliose de Lyme

Functional signs in patients consulting for presumed Lyme borreliosis

Marine Voitey^{1*}, Kévin Bouiller^{1, 2*}, Catherine Chirouze^{1, 2}, Damien Fournier³, Fabienne Bozon¹, Timothée Klopfenstein¹

¹ Service de Maladies Infectieuses et Tropicales, CHRU Besançon

² UMR CNRS 6249 Chrono-Environnement, Université de Bourgogne Franche-Comté, Besançon, France

³ Laboratoire de bactériologie, CHRU Besançon

* M. Voitey et K. Bouiller ont contribué de manière égale à l'écriture de l'article

Corresponding author Dr Bouiller Kévin

Service des Maladies Infectieuses et Tropicales, CHRU Besançon

Site Jean-Minjoz

2 boulevard Fleming, 25000 Besançon

E-mail : kbouiller@chu-besancon.fr

Numéro Tel : 0381219187

Numéro Fax : 0381218772

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RESUME

Contexte. Les signes fonctionnels en cas de borréliose de Lyme (BL) sont peu décrits en Europe. L'objectif était de décrire les signes fonctionnels des patients ayant une BL et de les comparer aux patients sans BL.

Patients et méthodes. Étude monocentrique, observationnelle et rétrospective. Étaient inclus tous les patients consultant pour suspicion de BL.

Résultats. De novembre 2015 à juin 2018, 355 patients ont été inclus (âge moyen de 51 ans, 52 % de femmes) dont 48 (14 %) avec BL : érythème migrant (42 %), forme disséminée précoce (50 % ; 35 % de neuroborrélioses) et forme disséminée tardive (8 %). Les signes fonctionnels les plus fréquents étaient douleurs neurogènes (23 %), arthralgies (23 %) et asthénie (17 %). L'ensemble des autres signes fonctionnels étaient ≤ 10 %. Trois cent-sept (86 %) patients n'avaient pas de BL. Les patients avec BL présentaient moins de signes fonctionnels (1,8 (+/-1,7) vs 3,6 (+/-2,5), $p < 0,001$) avec plus souvent une durée d'évolution < 3 mois (48 % des patients vs 16 %, $p < 0,001$). Ils décrivaient aussi moins souvent une asthénie (17 % vs 59 %, $p < 0,001$), des douleurs diffuses (10 % vs 31 %, $p = 0,003$), des myalgies (10 % vs 32 %, $p = 0,002$), des difficultés de mémorisation (4 % vs 16 %, $p = 0,03$), une irritabilité (2 % vs 23 %, $p < 0,001$) et une tristesse de l'humeur (0 % vs 16 %, $p = 0,003$).

ABSTRACT

Introduction. Little is known about the functional symptoms associated with Lyme borreliosis (LB) in Europe. We aimed to assess functional symptoms associated with presumed LB and to compare patients with and without confirmed LB.

Materials and methods. We performed a retrospective monocenter study. Patients consulting for presumed LB were included.

Results. Between November 2015 and June 2018, 355 patients were included (mean age: 51 years, 52% of women) of which 48 had LB: erythema migrans (42%), early disseminated LB (50%; 35% of neuroborreliosis cases), and late disseminated LB (8%). The most frequently reported functional symptoms were neuropathic pain (23%), arthralgia (23%), and asthenia (17%). Other functional symptoms were rare ($\leq 10\%$). Three hundred and seven (86%) patients did not have LB. Patients with confirmed LB reported fewer functional symptoms than patients without LB (1.8 (+/-1.7) vs 3.6 (+/-2.5), $p < 0.001$) with a shorter duration of symptoms (<3 months in 48% vs 16% of cases, $p < 0.001$). They less often reported asthenia (17% vs 59%, $p < 0.001$), widespread pain (10% vs 31%, $p = 0.003$), myalgia (10% vs 32%, $p = 0.002$), memory disorders (4% vs 16%, $p = 0.03$), irritability (2% vs 23%, $p < 0.001$), and sadness (0% vs 16%, $p = 0.003$).

Conclusion. In patients consulting for presumed LB, patients diagnosed with LB had fewer and shorter functional symptoms than patients without LB.

Introduction

The clinical expression of Lyme borreliosis (LB) is pleomorphic [1]. Clinical presentations of LB are defined in French and European guidelines [2,3].

Patients with LB may present with functional signs. However, little European data is available on functional signs in patients presenting with LB and available data is heterogeneous. A study performed in Slovenia prospectively included 892 patients presenting with erythema migrans (EM), and reported that 19% had asthenia, 15% had arthralgia, and 13% had myalgia [4]. A Danish retrospective study of 431 patients with Lyme neuroborreliosis reported asthenia in 15% of cases, arthromyalgia and cognitive complaints in 1% of cases [5]. A French study performed in Strasbourg described functional signs observed in 132 patients presenting with LB (all presentations), and reported that 25% of patients had asthenia and 5% experienced widespread pain [6]. More recently, a retrospective study performed in an infectious disease department in a Paris hospital focused on patients consulting for presumed LB. The median number of functional signs were three and patients had been presenting with these signs for a median duration of 16 months. The type of functional signs was not reported [7].

In our daily practice we observed that patients consulting for presumed LB present with multiple functional signs. We thus aimed to describe functional signs of patients presenting with LB and to compare them with functional signs reported by non-LB patients consulting for presumed LB.

Material and method

We performed a retrospective, observational, and monocenter study from November 2015 to June 2018 in the Franche-Comté region where the prevalence of LB is high [8]. All patients referred to infectious disease consultation for presumed LB were included in the study.

Data required for the study completion was collected from the medical files of patients: age, sex, comorbidities (Charlson score, history of rheumatologic and psychiatric disorders), exposure to tick bites, number of functional signs presented, type of functional signs and onset. Collected functional signs were pain (neuropathic pain defined by electric shocks and/or burns), arthralgia, myalgia, general pain, asthenia, headaches, paresthesia, insomnia, memory disorders, inability to concentrate, irritability, and sadness.

Patients were divided into two groups: LB group and non-LB group. In the LB group, patients meeting the European Union Concerted Action on Lyme Borreliosis (EUCALB) criteria were classified as confirmed LB cases; patients who did not meet such criteria [3] but whose LB diagnosis had been established by the infectious disease specialist were classified as probable LB cases. The non-LB group included patients for whom the LB diagnosis was not established. This group was divided into two subgroups: a subgroup of patients with a suspicion of differential diagnosis at the end of the infectious disease consultation, and a subgroup of patients for whom no diagnosis or diagnostic hypothesis was made.

We first described the functional signs presented by LB patients and non-LB patients. We then compared the functional signs of patients from the LB group with those of all patients from the non-LB group, and then with those of non-LB patients who received a differential diagnosis and finally with those of non-LB patients without any diagnosis. Usual descriptive statistics were used for the statistical analysis. Data was expressed as numbers, percentages (categorical variables), or mean. All variables were assessed using a univariate analysis:

qualitative variables were assessed with the Chi² test or Fisher's exact test, and continuous variables were assessed using Student's *t* test. A *p* value <0.05 was considered significant. We used the SPSS v21 software (IBM, Armonk, NY, USA).

Results

We included 355 patients.

LB patients

Forty-eight patients (14%) presented with LB (23 men, mean age: 54 years [+/-19 years]); including 40 with confirmed diagnosis and eight with probable diagnosis.

The eight patients with a probable diagnosis were: five patients with meningoradiculitis (suggestive clinical signs and symptoms, positive serology but the lumbar puncture was not performed and regression of symptoms was observed after treatment), one patient with myositis (persistent localized muscle pain with positive Lyme serology and cure after antibiotic therapy), two patients with sensory polyneuropathy (axonal involvement assessed by electromyogram, positive Lyme serology, no CSF pleocytosis, but positive index for intrathecal synthesis in CSF). Among confirmed LB patients, 20 patients (42%) had EM, 24 patients (50%) had an early disseminated presentation mainly with spinal and/or cranial meningoradiculitis (n=17, 35%), and four patients (8%) had a late disseminated presentation (Table I).

The mean number of functional signs per patient of the LB group was 1.85 (+/-1.68). The three main reported symptoms were neuropathic pain and arthralgia in 23% of cases respectively, and asthenia in 17% of cases (Table 1).

Non-LB group

The LB diagnosis was ruled out in 307/355 patients (86%). A differential diagnosis was made at the end of the consultation for 196 (64%) patients, mainly rheumatologic diseases (25.5%), psychiatric disorders (25%), neurological disorders (11%), infectious diseases (9.6%), and dermatological disorders (9.6%). No diagnosis was found or suggested at the end of the infectious disease consultation for 36% of patients.

The main functional signs presented by patients of the non-LB group were asthenia (59%), myalgia (32%), and general pain (31%).

Comparison of LB patients with non-LB patients

Both groups did not differ by sex ($p=0.970$) nor by mean age (54 ± 19 years vs. 50 ± 18 years, $p=0.13$).

Comorbidities assessed by the Charlson score were similar in the two groups. A higher prevalence of psychiatric disorders was observed in non-LB patients than in LB patients (14% vs. 4%, $p=0.053$), with a majority of depressive disorders (11% of non-LB patients). No difference was observed between the groups in terms of history of rheumatologic diseases.

LB patients were more frequently exposed to tick bites than non-LB patients, whether it be in their garden or in the forest (84% vs. 66%, $p=0.02$), and they more often reported recent tick bite, i.e. less than three months before the consultation (33% vs. 5%, $p<0.001$).

Patients from the LB group had fewer functional signs than those of the non-LB group ($1.85 (+/-1.68)$ vs. $3.55 (+/- 2.52)$, $p<0.001$). Thirty-one per cent of LB patients had at least three functional signs versus 60% of patients of the non-LB group ($p<0.001$). The onset of functional signs of LB patients was recent (<3 months before the consultation) (48% vs. 16%,

$p < 0.001$) and rarely dated from more than one year before, unlike non-LB patients (13% vs. 52%, $p < 0.001$).

Asthenia was less frequent in patients from the LB group than in those of the non-LB group (17% vs 59%, $p < 0.001$). LB patients also less frequently reported general pain (10% vs 31%, $p = 0.003$), myalgia (10% vs 32%, $p = 0.002$), memory disorders (4% vs 16%, $p = 0.027$), irritability (2% vs 23%, $p = 0.001$), and sadness (no LB patient vs 16%, $p = 0.003$). No difference was observed with arthralgia (23% vs. 22%, $p = 0.98$) and paresthesia (10% vs. 11%, $p = 0.945$). Neuropathic pain was more frequently observed in LB patients (23% vs. 13%, $p = 0.069$) (Table 2).

When comparing LB patients with non-LB patients who received a differential diagnosis, asthenia (17% vs 56%, $p < 0.001$), widespread pain (10% vs 29%, $p = 0.013$), insomnia (6.2% vs 24%, $p < 0.01$), irritability (2.1% vs 24%, $p < 0.01$), myalgia (10% vs 30%, $p = 0.011$), sadness (0% vs 18%, $p < 0.01$), and symptom duration < 3 months (48% vs 14%, $p < 0.001$) were statistically different.

Results were similar when comparing LB patients with non-LB patients who did not receive any diagnosis: asthenia (17% vs 64%, $p < 0.001$), widespread pain (10% vs 33%, $p < 0.02$), insomnia (6.2% vs 25%, $p = 0.013$), irritability (2.1% vs 20%, $p < 0.01$), myalgia (10% vs 35%, $p < 0.01$), sadness (0% vs 11%, $p < 0.019$), and symptom duration < 3 months (48% vs 18%, $p < 0.001$) were statistically different. However, the Charlson score was higher in the LB group (1.58 vs 1.08, $p = 0.043$).

Discussion

Functional signs in LB patients

Functional signs of LB patients included in our study were reported in 85% of cases, and were most often arthralgia (23%), neuropathic pain (23%), and asthenia (17%). Half of patients were presenting with symptoms for less than three months.

Distribution of the various LB presentations included in our study (42% of EM, 50% of early disseminated presentations with mostly Lyme neuroborreliosis cases [35%], and 8% of late disseminated presentations) was similar to that reported in European hospital cohorts. One should note that arthritis cases were far less frequent in our study compared with European literature data: 2% vs. 7% in a Swedish cohort of 1,471 patients, and 14% in Alsace, a neighboring region of Franche-Comté [6,9,10]. Table III details the frequency of functional signs reported in the literature by LB presentations in Europe. We observed the same proportion of functional signs by clinical presentations than the other studies: patients with EM had arthralgia or myalgia in 15% of cases and asthenia in 15% of cases. These figures are similar to European ones: respectively between 9%-18% and 13%-32% [4,6,11,12]. Patients presenting with Lyme neuroborreliosis had asthenia in 18% of cases, similar to findings reported in a Danish cohort of 431 patients where asthenia was observed in 15% of patients [5]. Unlike published data, arthralgia and myalgia were more frequent in our study: 30% and 6% of cases respectively versus 0.7% and 17% of cases [5,6]. We could not reach any conclusion on late disseminated presentations because of our small sample size (two acrodermatitis chronica atrophicans cases and two axonal sensory polyneuropathy cases). Acrodermatitis chronica atrophicans cases reported in the literature are often associated with neuropathic pain (25% of cases), but not with the other functional signs [13].

Irritability and sadness were rare in our cohort (2% of cases), similarly to literature data where these signs are also rarely reported (0%-16% of cases on average). Memory disorders and/or inability to concentrate were observed in 10% of our cohort, and were not more frequent in patients presenting with Lyme neuroborreliosis (12%, $p=0.832$). Little data is available in the European literature on these symptoms, but they also seem to be rarely reported (<3% of cases, even in cases of Lyme neuroborreliosis) [5]. This may be explained by the difficult collection of these signs because studies are most often retrospective. Memory disorders or inability to concentrate, irritability, and sadness may therefore be reported in patients presenting with LB; however, they were not that frequent and did not seem specific. The presence of one of those signs should therefore not guide physicians toward LB diagnosis.

Comparison of functional signs between LB patients and non-LB patients

Patients from the LB group had fewer functional signs than patients of the non-LB group. No study has so far precisely described the functional signs of patients consulting for presumed LB.

A recent clinical trial compared 200 patients with multiple EM with a control group (192 individuals, recruited among close relatives of cases). No difference was observed between the number of symptoms of patients with multiple EM and those of the control group, whether it be at inclusion or at the 6- and 12-month follow up [14]. However, by definition, the control group included healthy people unlike our non-LB patients who consulted for clinical signs and symptoms suggestive of LB.

Dersch *et al.* performed neurocognitive tests on 30 patients who had Lyme neuroborreliosis and on 35 control patients. They did not observe any difference in cognitive abilities [15].

One should note that the characteristics of our patients did not differ by age or comorbidities. History of rheumatologic diseases did not differ between the groups either; thus, the differences observed in terms of pain cannot be explained. History of psychiatric disorders seemed to be more frequent in the non-LB group. This may explain the higher frequency of irritability and sadness in this group.

Interestingly, some functional signs are more frequent in LB patients and may thus guide physicians toward the diagnosis. Although no significant difference was observed for arthralgia and paresthesia, the type of pain seemed to be different between the groups: LB patients seemed to more frequently experience neuropathic pain (23% vs. 13%, $p=0.069$) and less general pain or myalgia. However, such differences should be considered with caution. As functional signs are not considered criteria for LB, the number of patients with functional signs included in the non-LB group is "by definition" increased; and as radiculitis is an LB criteria, it also tends to increase the frequency of neuropathic pain in this group.

Another important limitation of our study was the absence of accurate and homogeneous diagnosis in the non-LB group of patients. No systematic multidisciplinary meeting was held, and patients were referred to a specialist based on the initial clinical presentation and on the infectious disease specialist's advice. Thus, in this group of patients, a differential diagnosis was reported in 196 (64%) patients who mainly had rheumatologic diseases (25.5%) and psychiatric disorders (25%) [16]. No diagnosis was established in 36% of patients. This data is similar to findings from two other French studies evaluating patients consulting for presumed LB [17,18].

However, the subgroup analysis revealed the same differences in terms of functional signs when comparing the LB group with the non-LB group but with a differential diagnosis or when comparing the LB group with the non-LB group without any diagnosis.

Moreover, most patients of our LB group had an early presentation of the disease for which functional signs are rather rare [6,19]. Disseminated presentations only accounted for 28/48 LB patients. However despite our small sample size, differences in functional signs persisted when comparing those 28 patients with the non-LB patients (n=307) (asthenia, $p<0.001$; general pain, $p=0.048$, irritability, $p=0.032$, myalgia, $p=0.039$; sadness, $p=0.021$). However, the number of functional signs was not different.

The retrospective collection of data may be responsible for the underestimation of functional signs in our study. We also did not use any quality of life scale and/or did not perform any neuropsychological evaluation to further assess cognitive complaints. However, physicians of our unit pay particular attention to patients consulting for presumed LB given the variety of possible differential diagnoses. All patients presenting with LB suspicion are assessed by a senior infectious disease specialist, who ask for a precise description of the patient's symptoms. A standardized grid for data collection is also completed by the senior physician during the consultation.

Despite our study limitations, we observed that functional signs not associated with LB are widely observed during consultations. On the one hand, patients may be faced with uncertainty at the end of the consultation with regard to the origin of their symptoms/signs and may sometimes feel that their problem has not been medically acknowledged. On the other hand, physicians face fears of not recognizing a somatic disease, of not being able to reassure patients given the lack of alternative diagnosis, and sometimes of alleviating

chronic symptoms; they may thus be responsible for over-medication. Recent polemics about Lyme borreliosis, mainly on the so-called “chronic” presentation of the disease and on the sensitivity of serological tests, make it an ideal diagnosis to explain every symptom. However, such reasoning is harmful to patients as differential diagnoses may be missed. Such behavior also goes against the basis of medical practice, i.e. evidence-based medicine.

Conclusion

Patients with LB present with asthenia and widespread pain in 15-20% of cases, with memory disorders and/or inability to concentrate in 10% of cases, but irritability and sadness are rarely observed. However, a recent history of tick bite and recent onset of symptoms are suggestive of LB.

Exposure to tick bites should be investigated by physicians when confronted with a presumed case of LB. However, the presence of numerous functional signs and the long duration of symptoms are not initial indicators of LB diagnosis. Caution is however required with patients presenting with neuropathic pain as they seem to be more frequently observed in cases of LB.

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Table 1. Functional signs in LB patients (n=48)**Tableau 1.** Signes fonctionnels chez les patients ayant une BL (n = 48)

Lyme borreliosis stage	Asthenia	Neuropathic pain	Arthralgia	Myalgia	Widespread pain	Memory disorders and/or inability to concentrate	Sadness and/or irritability
EM (20)	15% (3)	5% (1)	15% (3)	15% (3)	10% (2)	5% (1)	0
Early disseminated stage (24)	21% (5)	38% (9)	29% (7)	8% (2)	13% (3)	13% (3)	4% (1)
<i>Lyme neuroborreliosis (17)*</i>	18% (3)	53% (9)	30% (5)	6% (1)	12% (2)	12% (2)	6% (1)
<i>Other (7) **</i>	29% (2)	0	29% (2)	14% (1)	14% (1)	14% (1)	0
Late disseminated stage (4) ***	0	25% (1)	25% (1)	0	0	25% (1)	0
Total (48)	17% (8)	23% (11)	23% (11)	10% (5)	10% (5)	10% (5)	2% (1)

* Two patients with early Lyme neuroborreliosis also had another form of LB: one had EM and one had multiple EM.

** Early disseminated stage except for Lyme neuroborreliosis (n=7): three multiple EM cases, one arthritis case, one borrelial lymphocytoma case, one tongue papillitis case, one myositis case.

*** Late disseminated stage (n=4): two axonal sensory polyneuropathy cases, two acrodermatitis chronica atrophicans cases.

Table 2. Comparison of functional signs between LB patients and non-LB patients**Tableau 2.** Comparaison des signes fonctionnels entre les patients ayant une BL et ceux n'ayant pas de BL

Variable		LB (n=48)	No LB (n=307)	<i>p</i>
Sex	Female	52% (25/48)	52% (159/307)	0.970
	Male	48% (23/48)	48% (148/307)	
Age		54.3 (+/-18.7)	50.0 (+/-18.0)	0.132
Tick bite	≥1	82% (37/45)	72% (181/251)	0.156
	≥3	26% (10/39)	22% (45/202)	0.647
	≥10	23% (9/39)	19% (39/203)	0.579
	<3 months	33% (14/42)	5% (10/219)	<0.001
Exposure	All populations	84% (38/45)	66% (164/247)	0.016
	Forest	72% (28/39)	54% (126/233)	0.039
	Garden	51% (22/43)	33% (74/224)	0.023
	Occupational	14% (6/43)	17% (41/237)	0.589
Comorbidities	Charlson score	1.58 (+/-1.60)	1.24 (+/-1.38)	0.117
History of psychiatric disorders	All	4% (2/48)	14% (43/302)	0.053
	Depression	2% (1/48)	11% (34/302)	0.065
	Other	2% (1/48)	4% (12/302)	1
History of rheumatologic disorders	All	19% (9/48)	23% (69/302)	0.526
	Inflammatory diseases	8% (4/48)	5% (14/302)	0.288
	Mechanical diseases	13% (6/48)	19% (56/302)	0.308
History of EM		15% (7/48)	8% (23/307)	0.156
Onset of functional signs	<3 months	48% (23/48)	16% (45/286)	<0.001
	3-12 months	40% (19/48)	24% (69/286)	0.024
	≥1 year	13% (6/48)	52% (148/286)	<0.001

	≥10 years	2% (1/48)	8% (24/286)	0.229
Number of functional signs	All	1.85 (+/- 1.68)	3.55 (+/-2.52)	<0.001
	≥3	31% (15/48)	60% (183/307)	<0.001
Functional signs				
Asthenia		17% (8/48)	59% (182/307)	<0.001
General pain		10% (5/48)	31% (96/307)	0.003
Myalgia		10% (5/48)	32% (98/307)	0.002
Arthralgia		23% (11/48)	22% (66/307)	0.980
Neuropathic pain		23% (11/48)	13% (40/307)	0.069
Headaches		10% (5/48)	20% (62/307)	0.107
Paresthesia		10% (5/48)	11% (33/307)	0.945
Insomnia		6% (3/48)	25% (77/307)	0.004
Inability to concentrate		8% (4/48)	15% (47/307)	0.200
Memory disorders		4% (2/48)	16% (50/307)	0.027
Irritability		2% (1/48)	23% (71/307)	0.001
Sadness		0% (0/48)	16% (48/307)	0.003

Table III. Functional signs in LB patients (European literature data)

Tableau III. Signes fonctionnels en cas de BL (données de la littérature européenne)

Lyme borreliosis stage	Asthenia	Arthralgia	Myalgia	Memory disorders	Inability to concentrate
Erythema migrans					
<i>Our study</i>	15% (3/20)	15% (3/20)	15% (3/20)	5% (1/20)	5% (1/20)
France (<i>Lipsker et al.</i> 2001)	13% (7/53)	-	-	-	-
Slovenia (<i>Strle et al.</i> 2002)	19% (170/892)	15% (134/892)	13% (117/892)	-	-
Germany (<i>Weber et al.</i> 1986)	32% (33/104)	18% (19/104)	17% (18/104)	-	3% (3/104)
The Netherlands (<i>Kuiper et al.</i> 1994)	-	9% (7/77)	9% (7/77)	-	-
Early disseminated presentation					
Multiple erythema migrans					
Slovenia (<i>Stupica et al.</i> 2018)	26% (51/200)	22% (44/200)	11% (21/200)	-	-
Lyme neuroborreliosis					
<i>Our study</i>	18% (3/17)	30% (5/17)	6% (1/17)	12% (2/17)	12% (2/17)
France (<i>Lipsker et al.</i> 2001)	66% (19/29)	17% (5/29)*	-	-	-
Denmark (<i>Knudtzen et al.</i> 2017)	15% (65/431)	1% (3/431)	-	1% (6/431)	0% (2/431)

Germany (<i>Oschmann et al. 1998</i>)	-	2% (5/330)	13% (43/330)	-	-
Arthritis					
France (<i>Lipsker et al. 2001</i>)	33% (6/18)	-	-	-	-
Borrelial lymphocytoma					
Slovenia (<i>Maraspin et al. 2016</i>)	32% (46/144)	24% (35/144)	19% (28/144)	-	-
Late disseminated presentation					
Acrodermatitis chronica atrophicans					
France (<i>Lenormand et al. 2016</i>)	0% (0/20)	0% (0/20)	0% (0/20)	-	-
Sweden (<i>Kindstrand et al. 1997</i>)	-	-	11% (7/63)	-	-
Germany (<i>Aberer et al. 1987</i>)	-	9% (4/46)	-	-	-

* In this study, the term used was "flu-like syndrome" (instead of arthralgia and/or myalgia).