FOLIA MEDICA CRACOVIENSIA
Vol. LIX, 1, 2019: 5–14
PL ISSN 0015-5616
DOI: 10.24425/fmc.2019.128022

Analysis of cases of Lyme arthritis in patients hospitalized in Infectious Diseases Department, University Hospital in Cracow

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Abstract: Lyme disease is an emerging problem in Poland. Analysis has been undertaken of the medical documentation of 86 patients hospitalized in the Infectious Diseases Department, University Hospital in Cracow in 2013–2016, suspected of Lyme arthritis. It has especially considered medical history including potential exposure to the infection, detailed characteristics of the symptoms, diagnostic challenges and results of the treatment. Only some patients had a history of erythema migrans and not all of them recalled tick-bite. The majority of the patients had affected large joints, especially knee joints, and polyarthritis was rarely observed. Symptoms were resolved completely or partially after antibiotic treatment in most patients. The diagnosis of Lyme arthritis in areas endemic for Lyme disease is still a diagnostic challenge in patients with other rheumatic diseases, including osteoarthritis.

Key words: Lyme disease, Lyme arthritis, treatment of Lyme arthritis.

Introduction

There has been noticeable increase in the number of tick-borne diseases in Europe, Asia and North America in the past few years, with Lyme disease being of the highest incidence [1, 2]. This epidemiological data is similar in Poland. Due to the National

Institute of Hygiene, the number of reported cases of Lyme disease in Poland in 2017 was 21,528, and the incidence rate was 56.02/100,000 population and was higher compared to 2016 [3, 4].

Lyme arthritis (LA) most commonly manifests itself in one ore few joints with non-characteristic, non-specific symptoms that can be commonly found in other diseases and usually requires differential diagnosis [5]. In patients not suffering from LA antibodies, Borrelia burgdorferi sensu lato (B. burgdorferi s.l.) can be present, which might lead to over-diagnosis of this disease and to introducing unnecessary, long-lasting antibiotic therapy.

The aim of this paper was the analysis of the data of patients treated for LA with consideration of diagnosis difficulties and results of the treatment.

Materials and Methods

We have analyzed the medical documentation of 86 patients, average age 55 years, hospitalized in the Infectious Disease Department, University Hospital in Cracow in 2013–2016, suspected of LA. There were 38 men and 48 women in this group. Patients were excluded if they had any of the following conditions: malignancies, autoimmune diseases, diseases that require immunosuppressive treatment, inflammatory rheumatic diseases. Lyme disease was diagnosed and treated due to the recommendations of the Polish Society of Epidemiologists and Specialists of Infectious Diseases (PTEiLChZ) [6]. Antibodies were detected with enzyme-linked immunosorbent assay (test Elisa Biomedica, ELISA), positive or equivocal results were confirmed with Western blotting (test Western blot Aescu, WB). Tick bites, presence of erythema migrans (EM), possible and correct antibiotic treatment due to EM, period of time between exposure and beginning of the symptoms were analyzed in patients' medical history. Symptoms were analyzed considering pain and swelling of the joints, number of included joints, diagnosis of osteoarthritis. Patients were treated with ceftriaxone (2 g intravenously) or doxycycline (2 × 100 mg orally) for 28 days. The results of the treatment were analyzed in 2 groups of patients. The first group (group I) were 64 patients who were previously treated for LA with oral doxycycline 2 × 100 mg for 28 days with total or significant improvement. We consider as a significant improvement more than a 50% reduction in symptoms of pain/inflammation of the joints (in the patient's and physician's opinions). The second group (group II) included 22 patients who were not treated previously due to LA. Results for both groups were compared.

This paper is based on archival data from medical histories so the approval of Bioethical Commission is not required.

Results

In 2013–2016, 86 patients suspected of LA were hospitalized in the Infectious Disease Department, University Hospital, Cracow. Patients were complaining of chronic, 6 month-lasting joints pain. Positive IgG antibodies to B. burgdorferi s.l were detected in blood serum of this patients. In the analyzed group, 13 patients (15%) denied tick-bite in the past, 53 patients (62%) reported multiple tick-bites, 20 patients (23%) reported single tick-bite.

In the analyzed group, 45 patients (52%) reported the presence of EM in the past, and in this group 17 were treated with antibiotics in the correct way, 10 patients received treatment with a delay of 1–2 months, 18 patients despite reporting EM were not treated with antibiotics at all. 9 patients who were correctly treated with antibiotics due to EM noticed other tick bites after this treatment, but without the symptoms of early Lyme disease.

Table 1. Presence of EM in analyzed group.

No EM in medical history	41 (48%)
Presence of EM in medical history, not treated	18 (21%)
Presence of EM in medical history, treated	27 (31%)

The period of time between a tick-bite and the beginning of the joints symptoms in the group of patients treated for EM most commonly was 2–12 months (6 patients) and over 2 years (6 patients) and 2–12 moths in the group of patients not treated for EM.

In the analyzed group, all patients complained of joints pain. Symptoms including 1 joint were observed in 36 patients (42%); in 21 it was knee joint, symptoms including 2 joints were observed in 19 patients (22%), 3 joints in 13 patients (15%), 4 in 6 patients (7%), 5 in 8 patients (9%), over 5 joints in 4 patients (5%). In physical examinations, swelling of the joints were seen in 32 patients (37%) at the admission to the hospital.

In the analyzed group, pain was most commonly present in the knee joint (81 patients) and in the shoulder joint (51), least often in the hip joint (22 patients) and small joints of the hand (26 patients). Swelling most commonly was observed in the knee and foot joints. In the group of patients with affected knee joints, the highest incidence rate of osteoarthritis was observed.

Table 2. Localization and characteristic of the symptoms.

Localization	Pain	Swelling	Osteoarthritis
knee	81 (94%)	11	30
hip	22 (25%)	0	7
foot	39 (45%)	11	16
elbow	33 (38%)	1	11
wrist	30 (35%)	4	10
hand	26 (30%)	5	8
shoulder	51 (59%)	0	15

In all 86 patients qualified for the treatment presence of IgG antibodies to B. burgdorferi s.l. (ELISA and WB) was confirmed, the presence of IgM antibodies ELISA was seen in 39 (45%) patients with positive WB in 10 amongst them (12%).

A CRP level within the norms was observed in 68 patients (79%), was moderately increased in 8 patients (9%), and in 10 (12%) patients CRP level was above 10 mg/l, reaching 51 mg/l in 1 patient.

In the group of 86 patients who were qualified for the treatment, 81 were treated with ceftriaxone intravenously, the rest of them were treated with oral doxycycline. 64 patients (group I) were previously treated with oral doxycycline for LA. 48 of them observed than complete relief of the symptoms, 16 observed significant improvement. Recurrence of the symptoms occurred after 3–22 months. 22 patients were not treated previously with antibiotics (group II). All patients in group I were treated intravenously with 2 g ceftriaxone for 28 days, 17 patients in group II due to the contraindications for doxycycline received the same treatment, 5 patients in group II were treated with doxycycline.

After the treatment in group I, a complete release of symptoms was observed in 50 patients (78%), 14 patients (22%) reported significant improvement. In group II in 2 patients (9%) treated with ceftriaxone the symptoms remained the same, a complete improvement was observed in 13 patients (59%) and partial in 7 patients (32%).

In group I amongst those patients with a complete improvement after the first treatment, recurrence of the symptoms was observed after 3–6 months in 29 patients, in 14 after 6–12 months, in 4 after 1–2 years.

Out of 16 patients with significant improvement after the first treatment, recurrence of the symptoms was observed after 3–6 months in 12 patients, and in 4 after 6–12 months.

Discussion

An etiological factor of Lyme disease are spirochetes of the *B. burgdorferi s.l.* complex, transmitted by *Ixodes* species ticks. Until now, there has been recognised 18 genospecies, *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii* i *B. bavariensis* are human pathogens, *B. bissettii*, *B. valaisiana*, *B. lusitaniae*, *B. spielmanii* are being conidered as potential human pathogens [5]. Skin, nervous system, joints and heart might be affected in this disease. LA is most commonly caused by *B. burgdorferi sensu stricto*. In Europe most commonly *B. garinii* and *B. afzelii* are seen so LA is relatively rare, it occurs in 3–25% of patients [6]. Tick-bite is necessary for infection, some patients don't notice that fact though. Lack of tick-bite or EM presence in medical history doesn't rule out the possibility of Lyme disease [7, 8].

Enkelmann *et al.* stated that amongst patients who were diagnosed with Lyme disease 71% of patients reported tick-bite and most often these were patients diagnosed with early, localized stage of the infection. The second most popular group were patients with neuroborreliosis and the smallest group-patients with LA [9]. In the analyzed group, 15% didn't notice tick-bite, 62% noticed multiple tick-bites and 23% singular.

Considering the duration and character of the symptoms in Lyme disease, we can distinguish the early, localized stage — most commonly EM, early disseminated stage and the late, chronic stage [10, 11]. The first cases of Lyme disease were described in the 1970s in the USA by Steere *et al.*, and it was noticed that an increased number of cases of recurrent joint pain, most commonly knee joints, with joints swelling in the summer months [12]. Before that, similar cases were diagnosed as rheumatoid arthritis [13].

In research conducted by Huppertz *et al.* in the group of 62 children with LA, only one person reported previous EM [14].

Steer *et al.* in research about the early stage of Lyme disease didn't observe EM in 18% of patients despite the presence of other symptoms caused by Lyme disease [15].

In the analyzed group, 52% of patients reported EM in medical history. Due to the standards of PSEaDID, this symptom is present in about 80% of patients, so in the analyzed group it was observed less often [6].

In the research of natural course of the disease conducted by Steer *et al.* in USA amongst patients who were not treated for EM, LA was observed in about 60% of patients, symptoms occurred averagely after 6 months and were present in one or few large joints, most often in knee joints [7, 16].

In Nardelli *et al.* research it was stated that symptoms including joints appear most often after few weeks to few months after the infection [17].

In the analyzed group, amongst patients who were not treated for EM, the average time from tick-bite to the beginning of the symptoms was 2–12 months, amongst treated patients 2–12 months and over 2 years. In both groups, this period most often was 2–12 months, which is partially similar to other mentioned research. Correct treatment of EM prevents dissemination of the spirochetes and disseminated stage of the disease. In the group of 17 patients who were treated for EM, 9 of them reported another tick-bite after the treatment and could possibly be reinfected, another 8 didn't notice tick-bite but still they could possibly be bitten, especially by the nymph of the tick. In 10 patients treatment was delayed by 1–2 months, which had an important influence on the development of the disseminated stage of the infection.

Joints involvement in Lyme disease can be observed in both early and late stage of the disease [18]. The disease is diagnosed in patients with arthritis in one or few joints, most often in large joints [19, 20]. Knee joint is the most common location; rarely is it localized in the temporomandibular joint and joints of feet and hands. Symptoms are usually asymmetrical [14, 20–23]. In physical examination of patients with LA swelling of the affected joint, it can be seen that the skin over it is usually warmed up and typically it causes little or no pain with passive range of motion [7]. In some cases, migrating pain of joints, muscles, muscles attachments and enthesis can be observed. It correlates with the results of our analysis, most common localization of symptoms were large joints-knee joint (84%) and shoulder joint (59%). Presence of the symptoms including joints of palms (30%) and feet (45%) were observed in patients with symptoms including large joints at the same time.

In the course of Lyme disease, monoarthritis or oligoarthritis is most often observed [6, 7, 16, 20, 24, 25]. In cases where more than one joint is involved, the number of involved joints is usually 2–4 [6, 16, 20]. Polyarthritis is not characteristic for LA and requires differential diagnosis for possible rheumatological diseases [7].

In the analyzed group, joints pain was reported by all patients, swelling of joints in 37% of patients. We observed that the majority of patients reported symptoms including one joint only (42%), the smallest number of patients were those with symptoms in 5 or more joints (4.6%). Symptoms of arthritis might be constant or can exacerbate in time [26]. During the course of the disease episodes are becoming longer, especially over 2 years of infection duration [7].

The level of CRP in the course of the LA is within the norms or only slightly elevated [27]. In the analyzed group, this parameter was normal in 79% of patients, in 21% it was moderately elevated.

LA is diagnosed based on the symptoms and the presence of antibodies to B. burgdorferi s.l. in blood serum. Presence of antibodies to B. burgdorferi s.l. in people with no symptoms of Lyme disease is not enough reason for diagnosing this disease. In early stages of LA, there is a presence of IgM anitibodies and the level of IgG antibodies is increasing. In late stages of LA, the presence of IgM antibodies

has no diagnostic value [28, 29]. Serological testing of the synovial fluid is not recommended [30].

In the analyzed group, qualifications for treatment with antibiotic was based on the presence of symptoms and IgG antibodies to B.burgdorferi s.l. in blood serum. Some patients also were positive for IgM, but because symptoms were of at least 6 months duration it didn't have any diagnostic value.

According to the recommendations of PSEaDID, medication of choice in LA is doxycyline or ceftriaxone [6]. In some countries also, amoxicillin can be considered in LA treatment [6, 31]. There has been no accurate evaluation of using cefuroxim in this group of patients [8]. If the treatment is correct, it leads to the eradication of spirochetes and in most patients to resolution of arthritis [7]. In about 10% of patients, with HLA-DRB1 0401, HLA-DRB1 0404 and HLA DRB1 0101 immunophenotypes suffering from LA, despite antibiotic treatment chronic synovitis can be observed [13]. If the symptoms of LA persist for more than 3 months despite treatment, to rule out antibiotic-refractory arthritis and to confirm the necessity of continuing the treatment Synovial fluid PCR testing for *B. burgdorferi* DNA can be helpful [32]. In Poland this test has not been standardized [7].

In research by Huppertzi *et al.* in group of 62 children with LA, in 77% of them symptoms were resolved after 1 or 2 courses of antibiotic therapy [14].

According to available data, symptoms in most patients treated for LA are resolved after antibiotic therapy [33–35].

In the analyzed group, 64 patients (group I) were previously treated with doxycycline for LA. 75% of them noticed a complete improvement, 25% reported a partial improvement. Symptoms recurred after 3–12 months. 25% of patients were not previously treated with antibiotics (group II). All patients from group I and 17 patients from group II were treated with ceftriaxone, 5 patients from group II were treated with doxycycline. After the treatment in group I, 78% of patients noticed a complete resolution of the symptoms, 22% a partial improvement. In group II, 9% of patients didn't notice any improvement, complete relief of symptoms was reported by 59% and partial by 32%. In the group of patients with partial improvement after the treatment sometimes further relief might be observed in the next few months after the treatment [31].

Some of the patients in the analyzed group were also diagnosed with osteoarthritis, which was the reason of diagnosing difficulties. The incidence rate of osteoarthritis increases with age, in people over 55 years it is diagnosed in about 80%. Exacerbation of symptoms of osteoarthritis might lead to difficulties in estimation of the symptoms of LA [36, 37].

In the analyzed group, 32 patients were diagnosed with osteoarthritis, and in 30 of them the knee joint was involved. In these patients after the antibiotic treatment, relief of symptoms or partial improvement was observed, however in such cases condition

of the patient should be carefully evaluated before stating the diagnosis, especially due to the possible presence of antibodies against B.burgdorferi s.l.

The diagnosis of LA in endemic for Lyme disease areas is still a diagnostic challenge in patients with other inflammatory arthritides.

Conclusions

1. The results of our analysis confirm that some patients don't notice tick-bite, EM is not present in all patients.
2. Delayed antibiotic treatment of EM might cause the dissemination of infection with B.burgdorferi s.l.
3. Symptoms of LA usually affect large joints, especially knee joints.
4. In LA symptoms most often affect one to four joints.
5. In LA recurrence of the symptoms is possible, it indicates the need for long lasting antibiotic therapy.
6. High incidence rate of osteoarthritis, especially in people over 55 years of age and possible presence of antibodies against B.burgdorferi s.l. in people not suffering from LA is the reason of problems in diagnosing LA.

Conflict of interest

None declared.

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