

The Jarisch-Herxheimer reaction associated with doxycycline in a patient with Lyme arthritis

Svitlana Nykytyuk, Oksana Boyarchuk, Sergiy Klymnyuk, Sofiya Levenets

Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

Abstract

Objectives: The objective of this article was to present the clinical peculiarity of the Jarisch-Herxheimer reaction (JHR) during antibiotic treatment of Lyme arthritis.

Material and methods: Case study presentation as a basis for discussion, literature search of PubMed database particularly in the subject of combination of the JHR and Lyme borreliosis using the combination of words "Jarisch-Herxheimer reaction" and "Lyme borreliosis", "Lyme arthritis", "antibiotic treatment", "generalized inflammation", "cytokine production", "children", "increasing awareness"; discussion of the problem based on a clinical case and cited articles.

Results: The authors present a case of Lyme arthritis in a 13-year-old boy, as well as a discussion of clinical features of this complication of Lyme disease treatment as the Jarisch-Herxheimer reaction. On the 7th day of doxycycline treatment the patient's condition deteriorated: a low-grade fever occurred, and severe arthralgias with intense hip, ankle and cervical spine pain and myalgias developed. Erythrocyte sedimentation rate and C-reactive protein were elevated. The Jarisch-Herxheimer reaction was diagnosed. This complication was characterized by severity, long duration and marked signs of inflammation.

Conclusions: In the reviewed literature the Jarisch-Herxheimer reaction in patients with Lyme borreliosis is described more often in adults, with mild course and short duration of the disease. Based on the presented clinical picture this severe complication may also be associated with long duration and marked signs of inflammation. The authors suggest that informing health professionals about occurrence of the Jarisch-Herxheimer reaction should help physicians to distinguish it from allergic reactions or other conditions and improve treatment outcomes.

Key words: child, doxycycline, Lyme arthritis, Jarisch-Herxheimer reaction.

Introduction

Lyme disease (Lyme borreliosis) is a multisystem disease affecting primarily skin, nervous system, joints, or heart [1]. It is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by ticks of the genus *Ixodes* [2]. Lyme arthritis is the most common manifestation of the late stage of Lyme borreliosis: it is reported in a third of cases of borreliosis [2, 3].

Lyme arthritis was first described by Steere et al. [4], in 1977 in children and adults with oligoarticular arthritis living around Old Lyme, Connecticut. The endemic areas of Lyme borreliosis are North America and Central Europe.

Transient arthralgia manifests as early Lyme disease, and develops days to weeks after infection [5]. However, the early stages of Lyme borreliosis may be asymptomatic and in these cases arthritis can be the first clinical manifestation of the disease [1]. Lyme arthritis commonly occurs months later and is associated with innate and adaptive immune responses [6].

Lyme arthritis is treated with antibiotics for 2–4 weeks and in most cases patients recover [2, 5]. However, in a small number of patients, synovitis can persist for months to several years, even after 1–2 months of treatment with antibiotics, and it is antibiotic-refractory (or slowly resolving) Lyme arthritis [7].

Address for correspondence:

Svitlana Nykytyuk, Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, MaidanVoli 1, 46001 Ternopil, Ukraine, e-mail: svitlananyk@yahoo.com

Submitted: 30.03.2020; Accepted: 9.09.2020

On the other hand, antibiotic treatment in patients with spirochetal infections can cause the Jarisch-Herxheimer reaction (JHR) [8]. This complication develops up to 10 days, commonly within 24 hours after antibiotic treatment of Lyme disease, and is manifested by fever, chills, severe pain and skin rash [5]. Symptoms resolve a few hours later. The Jarisch-Herxheimer reaction is most common in patients with syphilis, but also occurs in patients with leptospirosis and relapsing fever [8].

Herein the authors present a case of Lyme arthritis in a 13-year-old boy who developed the Jarisch-Herxheimer reaction during treatment with doxycycline.

Material and methods

The objective of this article was to present the clinical peculiarity of the JHR during antibiotic treatment of Lyme arthritis.

Methods: case study presentation as a basis for discussion, literature search of PubMed database particularly in the subject of combination of the JHR and Lyme borreliosis using the combination of words “Jarisch-Herxheimer reaction” and “Lyme borreliosis”, “Lyme arthritis”, “antibiotic treatment”, “generalized inflammation”, “cytokine production”, “children”, “increasing awareness”; discussion of the problem based on the clinical case and cited articles.

Conclusion of the Commission on Bioethics of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine, dated 5th of January, 2020 (protocol No. 56).

Table I. Laboratory and ultrasound findings in the patient

Parameter	Lyme arthritis presentation	Jarisch-Herxheimer reaction
Hemoglobin, g/dl	13.5	10.1
Leukocytes, cells/ μ l	10,64	12,12
Platelets, cells/ μ l	388,000	429,000
ESR, mm/h	24	40–71
CRP, mg/dl	7.6–11	40.7
Lactate dehydrogenase, U/l	–	139
Rheumatoid factor, IU/ml	< 10	< 10
Antinuclear antibodies, titer		< 1: 100
Joints ultrasound	Left knee bursitis and synovitis	Left hip arthritis, left knee bursitis and synovitis
Synovial fluid culture	–	Negative

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate.

Results

Case report

A 13-year-old boy was admitted to the regional hospital with complaints of left knee swelling, hip, ankle and cervical spine pain.

From the history it is known that the first signs of left knee arthritis appeared 6 months before the hospital admission. Several days before the onset of the symptoms, the patient fell; therefore post-traumatic arthritis was suspected. The patient was treated by an orthopedist in the outpatient department with non-steroidal anti-inflammatory drugs (NSAIDs) longer than one month, but the effect was only slightly positive. Summarized laboratory and ultrasound findings are presented in Table I.

The patient was referred to a rheumatologist, who revealed a history of a tick bite 9 months before the onset of arthritis. The patient was treated with doxycycline (100 mg twice daily) after the tick bite for 4 days to prevent development of Lyme borreliosis. Erythema migrans and other early signs of infection were not reported.

Considering the history of a tick bite, the patient underwent serological testing for Lyme borreliosis. Enzyme immunoassays for specific anti-*Borrelia burgdorferi* IgM and IgG were positive (176.8 U/ml and 72.2 U/ml respectively) and Western blot analysis was positive for specific anti-*Borrelia burgdorferi* IgM and IgG antibodies too.

Oral doxycycline 100 mg twice daily was administered for 3 weeks. Within 7 days after starting antibiotic treatment the patient's condition deteriorated: a low-grade fever (37.3°C) occurred, and severe arthralgias with intense hip, ankle and cervical spine pain, myalgias developed. Antibiotic treatment was continued, IV prednisolone was prescribed in the dose of 1.5 mg/kg for 3 days and further NSAIDs were used to relieve pain. By the end of doxycycline treatment the symptoms slightly decreased, but did not resolve completely.

Therefore, the patient was referred to the regional hospital. Physical examination revealed swollen and painful left knee, the skin over the joint was hot. There was no tachycardia, and tachypnea and blood pressure were normal (Table I).

Taking into account fever and severe cervical spine pain we also excluded neuroborreliosis. Cerebrospinal fluid testing did not reveal pathological changes. Polymerase chain reaction (PCR) of cerebrospinal fluid did not detect *Borrelia burgdorferi* DNA, *Borrelia miyamotoi* DNA, *Anaplasma phagocytophilum* DNA, or tick-borne encephalitis virus RNA.

As there were high levels of CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate), the second antibiotic treatment with IV ceftriaxone in the dose of

2 g/day for 4 weeks was prescribed. During this treatment the patient's condition improved, signs of arthritis resolved and arthralgias decreased.

Discussion

The peculiarity of this case is the deterioration of the child's condition during the antibacterial therapy, which may indicate such a complication of Lyme disease treatment as the Jarisch-Herxheimer reaction. A deterioration in the patient's condition occurred on the 7th day of treatment with doxycycline, which can be interpreted as a Jarisch-Herxheimer reaction. Generally, this complication develops in 7–30% of patients with Lyme disease [8] up to 10 days after the beginning of the treatment [5]. It is reported in patients with syphilis more often (8–75%) [8].

The combination of such symptoms as fever, severe polyarthralgias, and myalgias can also indicate JHR in this patient. Other studies reported that the reactions in patients with Lyme disease were milder than in other diseases, without organ dysfunction or need for hospitalization [8]. The signs of a reaction include chills, high temperature, hypotension, nonpruritic, nonpalpable rash, tachycardia, nausea, headache, strengthening of existing or occurrence of new symptoms of the underlying disease [5, 8].

Some authors have observed delayed onset (on the 14th day) of the JHR in doxycycline-treated Lyme disease [9]. In that case, the complication was presented by malaise, facial flushing, gingival erythema, and increasing of erythema, swelling and pruritus. The unusual Jarisch-Herxheimer reaction response to doxycycline in a patient with chronic Lyme disease is described in another case report [10]. The patient described a low-grade fever, sore throat, sinus congestion, watery diarrhea, headache, stabbing pain in the upper back muscles, increased fasciculations and fatigue. These symptoms appeared after the second dose of doxycycline, and increased until the third day [10].

Another issue involves the duration of the Jarisch-Herxheimer reaction. In our reported case the signs slightly decreased within a few days, but had not completely resolved by the end of doxycycline treatment. Most authors noted that JHR is a favorable, self-limited complication [5, 8].

In some cases it resolved over 3 hours [9], but common symptoms and signs resolved within a few days [8, 9]. One study reported that the nasal congestion and accompanying symptoms remained acute until the 7th day of the doxycycline treatment, though the fatigue and loose stools persisted over 2 months [10]. Throughout of the doxycycline treatment, the patients' weight declined by 16 kg.

We also observed an increase of CRP and ESR after doxycycline treatment (40.7 mg/dl and 40 mm/h respectively) and they remained high during ceftriaxone treatment. Interestingly, we did not find data about the changes in the acute phase reactants in patients with JHR in the literature.

Despite the lack of doubt about Lyme arthritis, which was indicated by the typical clinical data (initial arthritis in knee joint, absent arthralgia before the onset of arthritis, history of a tick bite), and confirmed by laboratory tests prescribed according to the recommendations of the Centers for Disease Control and Prevention [5, 11, 12], and taking into account the long duration of clinical symptoms and laboratory tests (CRP, ESR), we could not exclude an autoimmune process or combined autoimmune disease. Antinuclear antibodies and HLA-B27 were performed and they were negative.

The pathogenesis of the JHR is not fully clear [9]. At first, the role of an endotoxin in the development of JHR was suggested [13], but later experimental studies showed that spirochetes do not have biologically active endotoxins [14].

The pathogenesis of JHR is based on the development of inflammation [8]. The genesis of inflammation is multifactorial. In the case of *Borrelia burgdorferi*, the outer surface protein A lipoprotein stimulates cells to produce transcription factors for cytokines [15]. Increases of TNF, interleukin (IL)-6, and IL-8 cytokines levels were reported in the Jarisch-Herxheimer reaction [8].

Hyperproduction of pro-inflammatory cytokines causes the development of clinical signs of JHR. Clinical presentation of JHR involves many organs and systems, and it can include myocardial injury, liver and renal dysfunction, acute respiratory distress syndrome, central nervous system dysfunction (seizures, unconsciousness, strokes, etc.) [8].

The described phenomenon is also relevant for rheumatologists. Macrophage activation syndrome can also be triggered by medications or an infection on the background of inflammation that causes a cytokine storm, which can result in tissue damage and multi-organ dysfunction [16].

Apoptosis in human monocytes after phagocytosis of *Borrelia* could also be contributed to the pathogenesis of the Jarisch-Herxheimer reaction [17]. Phagocytosed spirochetes can cause acute inflammation.

On the other hand, there is a suggestion that the increased level of cytokines is the result of the JHR rather than its cause [8]. Most studies have reported cases of the JHR that occurred in the early stage of Lyme disease [8, 9]. A single report refers to JHR in chronic Lyme disease, where the clinical picture differs from the one in early Lyme disease [10].

The Jarisch-Herxheimer reaction does not require interruption of antibiotic treatment as in the case of an allergic response, and treatment should be continued [5, 10, 18].

The researchers emphasize the low awareness of physicians of the Jarisch-Herxheimer reaction [10, 19]. Therefore, as its symptoms can present before antibiotic treatment, this complication is often unrecognized [8]. Furthermore, JHR is often mistaken for an allergic reaction [5, 8].

Overall, clinical manifestations of JHR are very variable. They can vary in expression, time of onset and duration and possibly they also can depend on the stage of Lyme disease. Inflammation and cytokine production may be reflected in significant changes of acute phase reactants.

Physician education can be an effective tool for increasing awareness about Lyme disease and the potential outcomes of treatment [19, 20]. The improvement of doctors' knowledge about JHR will help to enhance alertness and to avoid unnecessary prescriptions and concerns.

Conclusions

In this paper based on a case report the authors discuss clinical signs of the Jarisch-Herxheimer reaction associated with doxycycline treatment in a patient with chronic Lyme arthritis. In the reviewed literature the Jarisch-Herxheimer reaction in patients with Lyme borreliosis is described more often in adult patients with a mild course and short duration of the disease. In the present case this complication occurred in the opposite clinical situation. The information about the Jarisch-Herxheimer reaction may be important for physicians to distinguish it from allergic reactions or other conditions, and this may cause an improvement of safety of the treatment and better outcomes.

The authors declare no conflict of interest.

References

- Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. *Infect Dis Clin North Am* 2015; 29: 269-280, DOI: 10.1016/j.idc.2015.02.004.
- Staneek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. *Lancet* 2012; 379: 461-473, DOI: 10.1016/S0140-6736(11)60103-7.
- Bacon RM, Kugeler KJ, Mead PS, Centers for Disease Control and Prevention (CDC). Surveillance for Lyme disease – United States, 1992–2006. *MMWR Surveill Summ* 2008; 57: 1-9.
- Steere AC, Malawista SE, Snyderman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum* 1977; 20: 7-17, DOI: 10.1002/art.1780200102.
- Huppertz HL, Dressler F. Lyme disease. In: *Textbook of pediatric rheumatology*, Cassidy JT, Petty RE, Laxer RM, Lindsley CB (eds.). Saunders, Philadelphia 2005: 591-600.
- Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. *J Clin Invest* 2004; 113: 1093-1101, DOI: 10.1172/JCI21681.
- Steere AC, Angelis SM. Therapy for Lyme arthritis: strategies for the treatment of antibiotic – refractory arthritis. *Arthritis Rheum* 2006; 54: 3079-3086, DOI: 10.1002/art.22131.
- Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg* 2017; 96: 46-52, DOI: 10.4269/ajtmh.16-0434.
- Kadam P, Gregory NA, Zelger B, Carlson JA. Delayed onset of the Jarisch-Herxheimer reaction in doxycycline-treated disease: a case report and review of its histopathology and implications for pathogenesis. *Am J Dermatopathol* 2015; 37: e68-74, DOI: 0.1097/DAD.0000000000000093.
- Haney C, Nahata MC. Unique expression of chronic Lyme disease and Jarisch-Herxheimer reaction to doxycycline therapy in a young adult. *BMJ Case Rep* 2016; 2016: bcr2013009433, DOI: 10.1136/bcr-2013-009433.
- Centers for Disease Control and Prevention. Lyme disease (Borrelia burgdorferi): 2017 case definition – retrieved from: <https://wwwn.cdc.gov/nndss/conditions/lyme-disease/case-definition/2017/>.
- Nykytyuk S, Klymnyuk S, Levenets S. Laboratory diagnostics of Lyme borreliosis in children with ticks bites in Ternopil region. *Georgian Med News* 2019; 11: 32-36.
- Gelfand JA, Elin RJ, Berry FW, Frank MM. Endotoxemia associated with the Jarisch-Herxheimer reaction. *N Engl J Med* 1976; 295: 211-213.
- Takayama K, Rothenberg RJ, Barbour AG. Absence of lipopolysaccharide in the Lyme disease spirochete, *Borrelia burgdorferi*. *Infect Immun* 1987; 55: 2311-2313.
- Bulut Y, Faure E, Thomas L, et al. Cooperation of Toll-like receptor 2 and 6 for cellular activation by soluble tuberculosis factor and *Borrelia burgdorferi* outer surface protein A lipoprotein: role of toll-interacting protein and IL-1 receptor signaling molecules in Toll-like receptor 2 signaling. *J Immunol* 2001; 167: 987-994, DOI: 10.4049/jimmunol.167.2.987.
- Minoia F, Davi S, Horne A, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a Multinational, multicenter study of 362 patients. *Arthritis Rheumatol* 2014; 66: 3160-3169, DOI: 10.1002/art.38802.
- Cruz AR, Moore MW, La Vake CJ, et al. Phagocytosis of *Borrelia burgdorferi*, the Lyme disease spirochete, potentiates innate immune activation and induces apoptosis in human monocytes. *Infect Immun* 2008; 76: 56-70, DOI: 10.1128/IAI.01039-07.
- Boyarchuk O. Allergic manifestations of primary immunodeficiency diseases and its treatment approaches. *Asian J Pharm Clin Res* 2018; 11: 83-90, DOI: <https://doi.org/10.22159/ajpcr.2018.v11i11.29059>.
- Koton Y, Bisharat N. Tick-borne relapsing fever with severe Jarisch-Herxheimer reaction. *Isr Med Assoc J* 2018; 1: 62-63.
- Boyarchuk O, Volokha A, Hariyan T, et al. The impact of combining educational program with the improving of infrastructure to diagnose on early detection of primary immunodeficiencies in children. *Immunol Res* 2019; 67: 390-397, DOI: 10.1007/s12026-019-09103-w.