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Review article

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Clinical characteristics of patients with lyme arthritis diagnosed in children from Ternopil region

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Abstract

Objectives: *The article deals with clinical picture of Lyme arthritis (LA) and clinical features distinguishing this form of arthritis from other forms. The description of the characteristic features of arthritis based on laboratory and instrumental examinations of children was presented in the article. The clinical manifestation of LA is very changeable what makes diagnosis difficult to define. The aim of our study was to prove that LA should be treated with antibiotic therapy.*

Material and Methods: *The authors present two cases of arthritis in children on the background of the tick bite, and systemic juvenile idiopathic arthritis (SJIA). Lyme arthritis (LA) was found in 7.0% of 200 examined children. Case study presentation as a basis for discussion, a literature search of MEDLINE and Scopus database. A review of the examination of biomarkers among patients with LA and Rheumatoid arthritis according to MEDLINE via OVID, EMBASE, and Web of Science databases was conducted systematically and 21 examinations were taken for qualitative analysis.*

Results: *Clinical characteristics was defined by an increase in body temperature, persistent monoarthritis and synovitis. Serological studies (Elisa and Immunoblot assays) were predominant factors for establishment the diagnosis even in case of the absence of epidemiological history.*

Conclusions: *1. The investigation proved that LA is manifested by increasing body temperature, persistent mono arthritis, and synovitis. 2. There were presented that serological studies (Elisa and Immunoblot) are determining factors for diagnosis verification even in case of the absence of epidemiological history. 3. It was proved that genetic examination on HLA antigen B27 is necessary for differential diagnosis of arthritis. 4. The given investigation based on laboratory and instrumental examinations of children showed that Lyme arthritis treatment envisages antibiotic therapy and rheumatoid arthritis and requires non-steroid plus antibiotic therapy.*

Keywords: Children, Lyme Arthritis, Systemic Juvenile Idiopathic Arthritis, Antibiotic Therapy

Background

Due to the fact that epidemiological history is insufficiently investigated, hereditary and allergic history leads to wrong diagnosis and possible mistakes in the treatment of LA. It should be investigated an antibiotic resistance during the treatment of arthritis especially in pediatrics. Pediatricians working in endemic regions should be informed about the clinical characteristics and have a high index of suspicion for LA to prevent any misdiagnosis [1].

Materials and Methods

The purpose of this article is to present the clinical variability of arthritis. Methods: case study presentation as a basis for discussion, a literature search of MEDLINE and Scopus database. The analysis of medical records of patients undergoing treatment in infectious diagnostic department at Ternopil Regional Children's Hospital (Western Ukraine) was made in children aged between 9 and 14 years old. Inclusion criteria: patients with arthritis, presence of painfully swollen knees: epidemiological anamnesis, biomarkers of LA, Serological studies, Elisa, immunoblot assays. A review of the examination of biomarkers among patients with LA and Rheumatoid arthritis according to MEDLINE via OVID, EMBASE, and Web of Science databases was conducted systematically and 14 examinations were taken for qualitative analysis. Ethical approval: the study was approved by the ethical committee of I. Horbschevsky

Ternopil National Medical University (Ukraine) (Ethical Committee No 62, January 11, 2022) in compliance with the recommendations of the Declaration of Helsinki, 1964, amended by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. The study was conducted in Ternopil region (Western Ukraine) and consisted of two parts: during the first stage, we conducted a survey and during the second one laboratory examination of blood samples taken from 3 patients with the diagnosis arthritis and all necessary diagnostics were made. Study 1. Our goal is to examine children admitted to Ternopil Regional Children's Hospital with a tick bite. 200 children aged from1 to 16 years were examined and appropriate laboratory examination was carried out. Study 2. At this stage, the patients were examined with the use of all necessary clinical and laboratory tests including ultrasound assay of joints, magnetic resonance imaging, the examination of rheumatic tests (antistreptolysin- O, antinuclear antibodies (ANA), daily monitoring of ECG, ECHO cardiography, a two-stage immunological examination by Elisa and immunoblot assays were done. Genetic examination of HLAB27 was carried out 20 children suffered from extracutaneous disseminated LA were additionally examined. Results: Study 1. The average age of children bitten by ticks was 11.9 years. 200 children-residents of Ternopil region aged from 7 to 16 years admitted to Ternopil regional hospital with tick bites were examined. L A was diagnosed in 14 (7.0%) children (7 girls and 7 boys). Epidemiological history showed that 4% of children had tick bites, one person had a double tick bite and 4% of children had multiple tick bites (more than 2 times). 7 children (4.6%) were bitten by ticks in the lower extremities, 2% was bitten in the neck and 2 % was bitten in the head (near an ear) and one child was bitten in its abdomen. Those children suffered from headache and low-body temperature. 3% of cases had mild pain, itching at the site of the bite was in 2 children, short attention span was observed in 1% of cases, pain and partial limitation of movement in the hip joints were observed in 5 children, pain in the knee joint was observed in 3 children, an increase of lymph node was observed in 3 cases. The duration of pain syndrome was observed during the period from 1 to 6 months. A differential diagnosis was made with juvenile idiopathic arthritis, a disease caused by the Epstein-Barr virus and other viral infection. A history of the study showed that half of the children with arthritis had erythema migrans (EM) on the eve of the disease. EM developed at the site of the bite in one child, in 4 children it was developed in remote areas. However, it was not found in 4 surveyed cases. According to the results of our survey, the main symptoms of LA were monoarthritis, synovitis. Clinical characteristics of the disease was the next: intoxication and hyperthermic, arthralgia syndromes and headache. In 2 children, arthralgia lasted for a year, in one child it was during 5 months, accompanied by a heaviness in the legs and lymphadenitis, one person each, two patients experienced allergic reactions of immediate type (Quinke edema). Work (Study, Case) 2. Differential diagnosis is reflected in cases 1,2.

Case Presentation 1

The nine-year-old boy was admitted to the hospital with complaints of the left knee joint swelling; hip, ankle. The first signs of the left knee arthritis appeared 3 months before the hospital admission. Epidemiological history: A tick bite was 3 months ago in the lower extremity. Physical examination: He had pink color on his skin. On the front surface of the thigh redness, its location was 5.0x10 sm. The general condition of the patient was moderately severe due to intoxication, arthralgia and pain syndrome. Locus Morbi: the knee joints were symmetrical, the movements in the knee and other joints mobility was preserved. The patient's body temperature was 37.3°C. The heart rate was 72 beats per minute, the tones were muted, systolic murmurs at the apex, rhythmic. Auscultation of lungs vesicular breathing, 18 per minute. Blood pressure 110/70 mm/Hg.

The peculiarity of this case was the deterioration of the patient in 3 months after a tick bite. The migration of the pain in different joints and muscles appeared. The patient suffered from unbearable pain and his body temperature increased. Prescription of non-steroidal antiinflammatory drugs did not bring relief. Laboratory examinations: the results of the blood analysis was the following: leukocytosis was (12,500/µl), elevated Erythrocyte sedimentation rate (ESR) was (40 mm/h), thrombocytosis were (509 g/L), hemoglobin was (101 g/L) (norm up 115-155 g/L). Biochemical blood test remained normal. We also considered autoimmune and/or rheumatologic conditions. Rheumatic tests: C-reactive protein was 40.7 mg/l. Antistreptolysin-O (ASL-O) was 500 IU/ml, Rheumatoid factor was <10 IU/ml, representing an autoantibodies class A, G, M. Sialic acids was <2.0 mmol/L (norm up to 2.5 mmol/L) and anti-nuclear antibodies (ANAs) and an anti-extractable nuclear antigen (ENA) panel (JO-1 antibody, SSB, SSA, anti-Smith, ribonucleoprotein) were negative. Anti- B. burgdorgferi – antibodies IgM-176.79 U/ml., antibodies IgG-72.2 U/ml. We defined antigens in immunoblot: VLsE Borrelia bugdorferi (VlSe-Bb) 7, Flagellin (p41) 20, BmpA (p39) 8, OspC Borrelia afzelii (OspC Ba)36, Ospc Borrelia burgdorferi (ospC Bb) 31, Ospc Borrelia garinii (Ospc Bg) 50, Anti-human-IgM (IgM) 61. The result of the synovial fluid analysis on joint puncture was negative. Instrumental methods: ECG of the heart. It was observed tachycardia, incomplete blockade of the right bundle branch and myocardial hypoxia in the patient. Ultrasound examination of the joint: it was observed the evidence of the left hip joint arthritis, signs of synovitis and the left knee bursitis, Backer's cyst. Taking into consideration the patient's history of a tick bite, a positive Enzyme immunoassays for a specific anti-Borrelia burgdorferi IgM, a positive Western blot analysis for a specific anti-Borrelia burgdorferi IgM and IgG antibodies we estimated the diagnosis of Lyme borreliosis, its disseminated form, Lyme arthritis and Backer's cyst. Due to a sufficient clinical suspicion, he was prescribed amoxicillin 50 mg/kg per day during a 21-day course.

Case Presentation 2

The eight-year-old girl was admitted to the pediatric department because of the fever of an unknown origin, fatigue, morning stiffness during the 1st hour, a headache, the restriction of the movements, a disfiguration in the projection of the ankle-joint. Anamnesis: she had been ill during four years before. The general condition of a patient was a mild severity due to intoxication syndrome and pain symptoms. There were observed normal respiratory sounds in the patient. The skin under her eyes were pale with "shadows". The subcutaneous fat layer of the patient was developed evenly and moderately. The swelling was absent. The tongue was covered by white mucous. The

thyroid gland was enlarged. Lymph nodes were not palpable. The general condition of the patient was of moderate severity, her body temperature was 37,3°C. Heart rate was 56 bpm, the tones were preserved, some arrhythmia was present. Respiratory rate was 20 breaths per 1 min, auscultatory-vesicular. Blood pressure was 110/70 mm Hg. SpO2=99%. Physical examination revealed pain in ankle-joints with swelling. There was gait impaired due to the defeat of ankle-joints. The axis of the upper and lower limbs was correct. Threre was observed left side thoracic scoliosis. During palpation there was edema and pain in the area of the ankle-and-phalangeal joints. The patient had valgus deformity of fingers of both feet. Functional insufficiency of the joints of the first degree was found. Laboratory examinations: the results of the blood analysis were the following: leukocytosis (51.000/µl), thrombocytosis 674,100/µl, hemoglobin (124 g/L). Biochemical blood test was within normal quantities. Rheumatic tests: C-reactive protein was 0, Antistreptolysin-O (ASL-O) (–) IU/ml, Rheumatoid factor was <10 IU/ml, Seromucoid 3.6 Instrumental methods. Echocardiographic parameter was a transverse chord to the middle third in the left ventricular. EF was 66%. ECG signs of myocardial hypoxia. Heart rate was 56 bpm. Ultrasound examination of abdominal cavity organs: the presence of mild hepatosplenomegaly. Orthopedic status of the patient was the following: juvenile idiopathic arthritis, a polyarticular variant of the lesions joints of the ankle- and shoulder- joints. Left-sided thoracic scoliosis was observed in the girl. Diagnosis. Juvenile idiopathic arthritis, a polyarticular variant of the lesions joints of the ankle- and shoulder- joints. Sacrocudium arthroplasty, progressive course, ANA was positive, XRstage, Left-sided thoracic scoliosis. The two-stage method was used for confirmation of Lyme disease in patients with arthritis. Discussion: Two cases of arthritis observed in children were presented in the article. The scientific researchers reported that SJIA and LA developed equally in both sexes [2-4]. The age of patients at the beginning of the disease is from 7 to 16 years in our investigation. The case of arthritis of left knee in nine-year-old boy was presented in the article. The boy fell ill with this disease 3 months before being admitted to the hospital because with tick bite in anamnesis. The most common symptoms of the disease associated with Lyme arthritis and other infections are: symptoms of intoxication including headache, Fever/ chills, pain and arthralgia, muscle pain and rash [5].

Systemic symptoms including myalgia and arthralgia can accompany EM, especially in Bb and Bg infections [6]. Hematogenous dissemination of bacteria occurs within days to weeks following a tick bite; host-driven immune responses often lead to specific symptoms [1]. The range of LA complaints ranges from subjective joint pain to periodic bouts of arthritis and to chronic erosion joint diseases [2]. Other studies showed that the presence of similar symptom on the onset of the disease leads to misdiagnosis [4,7]. In the second case, the eight-year-old girl was admitted with complaints of fever of unknown origin, fatigue, morning stiffness during the first hour, headache, restriction of movements, a disfiguration in the projection of the anklejoint. When juvenile idiopathic arthritis can be suspected in a patient it can be diagnosed with an infectious disease that is Lyme arthritis in children [8]. The probable prevalence of LA is 31% overall and 45% in the presence of knee triage. Children with joint damage caused by Lyme disease are more likely to experience knee lesions, lower peripheral leukocytes and lower cell count of fiber in the joints; they are less likely to have a fever compared to children suffering from septic arthritis [9,10]. In our study, all patients had persistent pain joint syndrome. One child suffered from myalgia. It is commonly believed that fibromyalgia is a common disorder causing arthralgia (not true arthritis), fatigue and instability which are the cause of persistent patient complaints [3]. In the article, we provided our examinations of two patients diagnosed with synovitis. Differentiation of LA from acute infection to chronic synovitis can help to understand the essence of not only this form but other forms of chronic inflammatory arthritis including rheumatoid arthritis as well [11]. The second case differs from the other ones by the patient's age, presence of polyarthritis, fatigue, morning stiffness that is common for sJIA and the onset of the disease was with a fever of unknown origin, arthritis but without typical rash. Evanescent rash occurred in 81% of patients with sJIA [12]. A high level of ANA and high titer RF are the markers of JIA is a chronic inflammatory disease in childhood that can lead to long-term morbidities such as uveitis, osteoporosis, depression, poor pain control and even severe disability due to joint damage as can be seen in second case [11]. Taking into account an increase of acute-phase protein levels in the first case found in patients with LA, the analysis of early LB-associated proteins found to be acute phase proteins (C-reactive protein, AS-O) as biomarkers of inflammation which can react in a few hours after borrelia enters the skin [13]. In response to infection, local inflammatory cells secrete cytokines into the bloodstream [14], stimulating liver cells to increase (or decrease) APP production that helps to clean the body from pathogens or inhibit their reproduction inside. The development of arthritis is partially dependent on spirochetal factors including the ribosomal spacer type and the sequence of outer surface protein C [5]. LA diagnosis usually needs a two-stage diagnostic approach of immunoassay followed by confirmation assay or immunoblot. The most sensitive antigen for IgM detection is OspC B. afzelii and IgG-VlsE respectively [15]. According to the manufacturer's recommendations, it is the OspC borrelia antigen that is most sensitive to detecting relevant IgM [16]. Most patients with Lyme arthritis responded well to standard (unidox) courses of antibiotic therapy but in 2 patients, strains of pathogens were resistant to antimicrobial treatment. There were symptoms of inflammation, synovitis (especially the knee joint) lasted for a long time, so the patients were prescribed the repeated courses of antibiotic therapy [17]. Large-scale analytical approaches to the study of the quantitative expression of genes (transcriptomics), proteins (proteomics) and metabolomics in Lyme borreliosis have recently created the potential for prediction in the development of the disease of the role of biomarkers at different stages of the disease and received after the treatment [18]. On the other hand, currently, there is no enough evidence for genetic testing. HLAB27 test wass positive in two patients. The presence of HLA-B27 was associated with certain autoimmune and immunemediated diseases including ankylosing spondylitis which causes inflammation of the bones in your spine, reactive arthritis. (Human leukocyte antigen B27) is of the first class surface antigen encoded by the B locus in the major histocompatibility complex on chromosome 6 and presents antigenic peptides to T cells. HLA-B27 is strongly associated with ankylosing

spondylitis and other associated inflammatory diseases referred to as "spondyloarthropathies") [18]. Additionally, B.burgdorferi epitopes may be involved in the development of antibioticresistant Lyme arthritis. OspA163-175 remains the only known recognized epitope of BB and related diseases [1]. In most patients, arthritis is treated with antibiotics. LA research in Southern Norway shows that the disease is benign which can be successfully treated with antibiotics, even in patients who received GK before taking antibiotics [19]. According to a scientific research, antibiotic-resistant LA may be the result of B. burgdorferi – induced autoimmunity in the affected joints. Such patients with antibiotic-resistant arthritis typically have certain HLA-DRB1 molecules that bind the epitope B. burgdorferi to the outer surface (OspA163-175) and cellular and humoral immune response to OspA more than in patients with antibiotic-reactive arthritis [20,21].

LA usually manifests itself as acute inflammatory monoarthritis. The presentation of symptoms without proximity to the time of the tick bite can lead to a delay in diagnosis. Delayed serology for Lyme disease may complicate the diagnosis of arthritis, especially in endemic areas regarding Lyme disease [11, 21]. Analysis of clinical cases allows you to identify problems, and plan future research, which may change the understanding of the consequences of the disease.

Conclusion

1. The investigation proved that LA is manifested by increasing body temperature, persistent mono arthritis and synovitis.
2. There were presented that serological studies (Elisa and Immunoblot) are determining factors for diagnosis verification even in case of the absence of epidemiological history.
3. It was proved that genetic examination on HLA antigen B27 is necessary for differential diagnosis of arthritis.
4. The given investigation based on laboratory and instrumental examinations of children showed that Lyme arthritis treatment envisages antibiotic therapy and rheumatoid arthritis and requires non-steroid plus antibiotic therapy. Conflict of Interest: The authors declare that they have no conflict of interest.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Svitlana Oleksiivna Nykytyuk-formal analysis, writing.
Sergiy Ivanovuch Klymnyuk-conceptualization, original draft, writing.

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