CLINICAL CASE OF IXODES TICK-BORNE BORRELIOSIS WITH DEVELOPMENT A-V BLOCKADE AND IMPLANTATION OF THE PACEMAKER

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Borreliosis is an infectious transmissible natural-focal disease caused by borrelia of borrelia burgdorferi sensu lato group and transmitted by ixodic ticks. In the article a clinical case of chronic ixodic tick-borne borreliosis is described with the primary damage to the heart, joints and with polyneuropathy of extremities. The described clinical case is interesting on the one hand by demonstration of peculiarities of the heart damage associated with ixodic tick-borne borreliosis which finally lead to transient III degree A-V block with episodes of asystole up to 5.5 s and to implantation of continuous pacemaker. On the other hand, surprising in XXI century is the fact that despite a wide availability of high-tech methods of diagnostics and treatment in any field of medicine, the ixodic tick-borne borreliosis was identified only in 6 years after the moment of manifestations of clinical symptoms.

Keywords: *ixodic tick-borne borreliosis, A-V block, pacemaker, arthritis, polyneuropathy.*

Ixodic tick-borne borrelioses (ITBB) make a group of infectious transmissible natural-focal diseases caused by borrelias of *borrelia burgdorferi sensu lato* group and transmitted by ixodic ticks. Clinically the disease runs with the primary lesions of skin, damages to the nervous system, musculo-skeletal apparatus, the heart, and is characterized by tendency to chronic and also to latent course [1]. In Russia the infection was first serologically verified in 1985 in the Northwestern region [2]. Nowadays the highest incidence of tick-borne borreliosis in the Russian territory is noted in Tver – 47%. The lowest incidence of the disease is in the Arkhangelsk region (0.3%). The incidence of tick-borne borreliosis in Ryazan is 13% [3,4]. Borrelia are Gram-negative spiral-shaped spirochetes. In the territory of Russia 4 genospecies are proved to be pathogenic for humans: *b.burgdorferi sensu stricto, b.garinii, b.afzelii* and *b.miyamatoi.* Genotypic peculiarities of the agent are clearly reflected in clinical presentation of ITBB with polymorphous character of clinical manifestations which depend on the etiology and in a number of cases may create difficulties in diagnosis.

Borrelia most commonly enter a human organism with saliva of a female tick in a bite. Borrelia may be transmitted through tick's feces if they get on the skin and are rubbed into the skin in scratching. Less commonly borrelia may be transmitted from animals to humans through raw goat milk or milk products not subjected to thermal processing. Incubation period lasts about 30 days. Reaction of a human organism to borrelia depends not only on the pathogenic properties of spirochete, but in many aspects on the genetic predisposition of response of the immune system. In ITBB there may be several ways of realization of infectious process. In most cases the disease in an infected individual is neutralized in the incubational or initial period with unnoticeable clinical manifestations of the infectious process. In other cases the disease develops with all characteristic manifestations – symptomatic (clinical) forms. In some cases the infection takes a latent form. ITBB may also

be characterized by a chronic infection which may develop both after a clinical stage of acute and subacute borreliosis, and after a period of latent infection [5,6].

IIBB, like any other infectious disease, is characterized by a cyclic course. In clinical picture three stages are distinguished. The first stage is a local infection. The most common symptom in the initial period is appearance of erythema around the primary affect – a site of the previous suction of an ixodic tick. Erythema may be accompanied by subjective sensations (itch, pain, burning). The hyperemized zone gradually increases in size – up to 5-15 cm to the periphery, sometimes up to 50 cm in diameter (hence, the term commonly encountered in literature – "migrating" erythema). In several days the central part of erythema usually turns pale and erythema takes the form of a ring for which reason erythema in ITBB is often called "annular" erythema, although there may be solid erythema with the same rate of occurrence. Without treatment erythema persists within 3-4 weeks and disappears. Infectious inflammatory alterations of skin of other etiology do not show such alterations which permits to consider migrating erythema a reliable clinical marker of ITBB. There exist both erythematous and non-erythematous variants of the course of the disease at the stage of local infection. Both variants are characterized by symptoms of systemic infectious intoxication [7,8].

The second stage is dissemination of the agent. It occurs in 1-3 months. On the distant parts of skin multiple erythematous elements may appear and a benign lymphocytoma. A characteristic sign is damage to the nervous system in the form of serous meningoencephalitis, neuropathy of cranial nerves, radiculoneuritis [9-12]. Myocarditis and pericarditis develop. Damage to the musculo-skeletal system is characterized by arthralgia, mono- and oligoarthritis usually of large joints, less often of small joints of wrists and feet, by inflammation of periarticular tissues (tendinites, tendovaginites, myosites) [13,14].

The third stage is a chronic course. It starts in 6-24 months after the onset of the disease. The stage is characterized by a progressing chronic inflammation of skin, joints, nervous system, the heart and less often of other organs leading to their atrophic and degenerative damages. Chronic ITBB may take a progredient course (with continually progressing signs of the disease in dynamics without remissions) or recurrent course with remission periods of different duration. Damage to the central nervous system may present with clinical signs of asthenovegetative syndrome, encephalomyelitis, multiple sclerosis, mental disorders, epileptiform fits. Damages to cranial nerves are noted (of vestibulocochlear and optic nerves) with stable derangement of their functions. Damage to the peripheral nervous system is manifested by polyradiculoneurites, polyneuropathy [15-19]. Arthrites in chronic ITBB are mostly characterized by damage to one or two large vessels, usually of one or both knee joints. Specific lesions of skin are noted in the form of a chronic atrophic acrodermitis.

In diagnostics of ITBB clinico-epidemiological diagnosis is reasonable. The following should be taken into account: stay of the patient in endemic regions, mention of visiting a forest in the medical history, the fact of suction of a tick, correspondence between the season and the onset of the disease, drinking raw goat milk. Identification in a patient of a characteristic migrating erythema associated with the epidemiological history, permits to diagnose ITBB on the basis of only clinical data. For etiological verification of the causative agent a wide range of microbiological tests are used (microscopic methods for detection of borrelia in different biological media, isolation of borrelia on nutritive media, detection of DNA molecule of borrelia in a biological sample in polymerase chain reaction). However, none of these methods possesses absolute sensitivity. There are clinical situations, where serological methods of diagnostics are more preferable. In view of the polymorphous clinical presentation of ITBB at the stages of discrimination and chronic infection, differential diagnosis is based first of all on serological methods.

Nowadays a two-step serological diagnostics of ITBB is used that suggests a sequential use of enzyme immunoassay (EIA) and of immune blotting. The first step permits

to determine the presence of specific antibodies to borrelia [20,21].

The second step determines specificity of IgG or IgM to certain proteins of borrelia (western-blot and immune chip methods). To exclude probable false-positive results, western-blot and immune chip methods are used that permit to detect specific antibodies against certain borrelia antigens. If EIA is negative, there is no need in more detailed examination with use of western-blot and immune chip because the result is very likely to be also negative [22-24].

Etiotropic treatment of ITBB is based on use of antibacterial drugs. The choice of an antibiotic is defined by its ability to penetrate organs, tissues and reach sufficient concentration there for action on the causative agent. Duration of treatment course is determined by the stage of the disease [25].

A clinical case is presented. A female patient X. of 46 years old referred to a rheumatologist in December 2014 with complaints of intensive pain in the left knee joint more evident in the morning hours, swelling of the left knee joint and restriction of flexion in the knee joint due to pain; moderate pain in both knee joints in intensive physical activity.

From medical history: in August 2008 the patient was several times bitten by ticks (she lives in the country side). In September 2008 a red spot appeared on the left shin which gradually expanded along the periphery, spread to the middle of hip and reached 60 cm in dimeter. She referred to dermatovenerologic dispensary where the diagnosis of dermatitis of unclear etiology was made; ITBB was not suspected. After treatment with topic steroids, erythema disappeared in a month. In August 2009 there appeared pain in the right knee joint with inflammatory rhythm, swelling of the joint, no hyperemia of skin above the joint. The surgeon to whom the patient referred for medical assistance diagnosed II stage gonarthrosis of the right knee joint, reactive synovitis. Synovitis phenomena were alleviated by intra-articular introduction of betamethasone. In September 2012 synovitis of the right knee joint reappeared and again was corrected by intra-articular introduction of betamethasone. Starting from January 2013 the patient felt moderate pain in the knee joints in intensive physical activity, in March 2013 episodes of brief dizziness, tinnitus, loss of consciousness appeared. The patient was observed by a neurologist with the diagnosis of vertebrobasilar insufficiency of spondylogenic character. Treatment with betahistine, drugs of neurometabolic effect and vasodilating drugs gave no effect, the above mentioned complains persisted. Differential-diagnostic examination evaluated the symptoms as a probable manifestation of Morgagni-Adams-Stokes syndrome, Holter monitoring was recommended which revealed (03.06.2014) transient A-V block with asystolic pauses up to 5.5 sec. For urgent indications the patient was hospitalized to Ryazan Regional Cardiologic Dispensary. Routine clinical and laboratory examination was conducted (common blood analysis, common urine analysis, biochemical blood analysis with evaluation of acute phase parameters, tests for biomarkers of myocardial necrosis and for antibodies to myocardium (< 1/10 against the norm < 1/10). Instrumental examination – ECG, EchoCG (dimensions of the heart chamber within the norm, structure and functions of the valves unchanged, contractility of the left ventricular myocardium not impaired), Holter ECG monitoring was repeated. Magnetic resonance tomography (MRT) of the heart including that with gadolinium enhancement, endomyocardial biopsy were not conducted due to absence of technical means. In result of conducted examination the following diagnosis was established: postmyocarditic cardiosclerosis, transient A-V block with asystoles up to 5.5 sec. On 16.06.2014 the patient was implanted Esprit DR model dual chamber pacemaker in DDD AV Hyst mode in the National Pirogov Medical Surgical Center, after which symptoms of Morgagni-Adams-Stokes syndrome disappeared. In December 2014 synovitis of the left knee joint reappeared which was the cause to consult a rheumatologist.

Life history: heredity: essential hypertension, IHD (III functional class exertional angina), chronic heart failure in mother. Allergological and gynecological history without peculiarities. Accompanying diseases: autoimmune thyroiditis, medical drug-

induced euthyroidism; I stage bilateral coxarthrosis; dorsopathy due to dystrophic-degenerative alterations in the cervical and lumbar sections of the spine, hernial form with syndrome of cervicalgia, lumbodynias with a moderate myotonic syndrome.

At the moment of examination by rheumatologist the condition was satisfactory. Clear consciousness, active position. Height 170 cm, weight 90.0 kg, body mass index 31.1 kg/m^2. Body temperature in the armpit 36.7°C. Skin and mucous membranes of usual color, no rash. Head, neck, eyes, ears, nose, the posterior pharyngeal wall without visible pathology. The chest of cylindrical shape. In lungs vesicular breathing, no rales. Respiratory rate 18 per minute. Heart sounds clear, no murmurs, regular rhythm with HR 60/min. AP 110/70 mm Hg. The tongue moist, clean. The abdomen without visible alterations, soft and painless to palpation, auscultation without peculiarities. The liver and spleen not enlarged. Regular defecations, shaped stools of brown color. No tenderness to percussion on both sides. Free, painless urination. Adequate diuresis. Thyroid gland, peripheral lymphatic nodes not enlarged.

Arthrological status: palpation reveals swelling and pain in the left knee joint. Hyperthermia of skin above the joint, no hyperemia. Active movements in the left joint are restricted by pain. Passive movements in full volume, but painful. In the right knee joint crepitation in palpation is noted. Other joints without peculiarities.

Neurological status: complaints of "creeping sensations" in legs, numbness in arms; feeling of numbness along the inner surface of the left knee joint, a feeling of the outward rotation of the leg in walking. In communication the patient is "tenacious", concentrated of her feelings. Intellect, memory unchanged. No meningeal signs. Cranial nerves: pupils D=S, photoreactions preserved, eyeballs move in full volume. No nystagmus. Face sensitivity unchanged. Nasolabial folds symmetrical, the tongue on the median line, swallowing unchanged. Reduction in ankle and carporadial reflexes, alteration in sensitivity in the form of "sock", "glove" hyposthesia (of polyneuritic type). The tone unchanged. Disorder in the sensitivity in the zone of innervation of the left obturator nerve. Stable in Romberg's maneuver, finger-nose test, heel-to-knee-to-toe test are correct. Physiological spinal curvatures smoothed, hypertone of paravertebral muscles, trigger points in paravertebral zones of cervical, lumbar sections of spine. "Run off" symptom on the right. Lasegue symptom negative. Howship-Romberg phenomenon positive. Painfulness to palpation in the point of the obturator canal on the left. Conclusion: polyneuropathy of extremities with sensory disorders. Neurology of the left obturator nerve with moderate painful and myotonic syndrome.

Differential diagnosis included: reactive infectious arthritis, first of all ITBB, and also spondyloarthrites, diffuse diseases of connective tissue.

CBC revealed leukopenia, neutropenia: leukocytes – 2.87x10^9/l, neutrophils – 1.21x10^9/l, ESR – 3 mm/hour (by Westergren method). In biochemical blood test, in common urine test no pathologies were found. Examination of immune status showed reduction in CD45/CD3-CD16+CD56+ (NK-cells) – 0,102x10^9/l (norm 0,3-0,6x10^9/l). Antinuclear factor determined by indirect immunofluorescence method on HEp-2-cells preparations <1/160 (norm <1/160). Antibodies of IgG class to double helix DNA <20 ME/ml (norm <20 ME/ml). X-ray of knee and hip joins showed signs of II stage bilateral gonarthrosis and I stage coxarthrosis (by Kellgren and Lawrence). Ultrasound of knee joints: signs of osteoarthrosis, degenerative-dystrophic changes of menisci, infrapatellar bursitis (clergyman's knee). MRT of the left knee joint: signs of osteoarthrosis, degenerative-dystrophic changes of menisci, synovitis. MRT of iliosacral joints: no pathological alterations. MRT of the brain and cerebral arteries (28.03.2014, before implantation of cardiac pacemaker): no data indicating focal and diffuse changes in the brain matter, but mild internal hydrocephaly; MRA: variant of development of Willis' artery in the form of reduction of blood flow and narrowing of the lumen of posterior communicating cerebral arteries and hypoplasia of the intracranial part of the left vertebral artery. In the urogenital scrape no *ureaplasma urealiticum* and *clamydia trachomatis* were detected by PCR.

Method of passive hemagglutination reaction did not reveal *anti-brucella* species and anti-*listeria* monocytogenes IgG and M. Using IEA method, anti-*borrelia burgdorferi* IgG – 163.9 Un/ml were obtained from the blood serum. By immune chip method IgG antibodies to antigens of *borrelia afzelii* and *borrelia garinii* were isolated (p17, p39, p41, p58, p100, V1sE, BBK32). Western blot method revealed IgG to specific antigens of *borrelia afzelii* and *borrelia garinii* (p17, p19, p21, p25, p39, V1sE). By immune chip and Western blot methods no IgM antibodies to *borrelia afzelii* and *borrelia garini* were detected.

Thus, taking into account presence of antibodies to *borrelia burgdorferi* determined by IEA, immune chip and western blot methods, the fact of tick's bite with associated annular migrating erythema in the history, and after exclusion of other causes for pathological processes in the heart, vessels, and peripheral nervous system which could cause the existing clinical symptoms, the patient was diagnosed with chronic tick-borne borreliosis, severe recurrent course with the primary damage to the heart (postmyocarditic cardiosclerosis, III degree transient A-V block, implantation of pacemaker 16.06.2014), to the joints (recurrent arthritis of the knee joints, secondary bilateral II stage gonarthrosis), polyneuropathy of extremities with sensory disorders.

A course of treatment with minocycline 100 mg 2 times a day perorally for 3 weeks, then 50 mg 2 times a day for 2 weeks and diclofenac 50 mg 3 times a day was prescribed by infectiologist [26]. No clinical effects followed, recurrence of synovitis of the left knee occurred. At present the patient remains under observation.

The described clinical case is interesting, on the one hand, from the point of view of demonstration of the heart damage associated with ITBB that finally resulted in transient III degree A-V block with episodes of asystole up to 5.5.sec and implantation of continuous electrical pacemaker [27]. Unfortunately, lack of data does not permit to answer a question if the developed symptoms are associated with a recurrence of chronic myocarditis or with postmyocarditic cardiosclerosis. On the other hand, surprising in XXI century is the fact that despite a wide availability of high-tech methods of diagnostic and treatment in any sphere of medical activity, ITBB was identified only in 6 years after manifestations of clinical symptoms.

In conclusion the authors would like to note that the given clinical case clearly shows that in treatment of a "simple", at the first sight, patient, one should not forget academic approach and should be guided by edifications of a great Russian therapist M.Ya. Mudrov, such as "correctly taken history is half the diagnosis", "it is not the disease but the patient that should be treated", "ailment is not a local disease, but a manifestation of a systemic derangement in an organism". Practical application of these edifications would permit not to ignore a tick's bite followed by migrating erythema in the patient's history, but to combine the existing symptoms into a single whole and suggest that they may be manifestations not of several diseases, but of one disease, which would enable making correct diagnosis in the earlier period thus preventing development of a life-threatening complication.

Authors have no conflict of interest to declare.

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