Family Practice
Family Practice

Issue 6 (2), December 2017

VOLUME 34

Oxford University Press
2017
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Usage of wobenzym in complex therapy of lyme disease

Abstract: Duration of main clinical attributes and frequency of recurrent and chronic forms occurrence during the use of wobenzym in complex therapy were analyzed in 87 patients with fixed diagnosis of Lyme disease. It was established that their duration shortened in 2,2 times (p<0,05). Accounting the data received the usage of wobenzym which potentiates the effect of antibiotics in complex therapy of Lyme disease was validated.

Keywords: Lyme disease, Borrelia, etiotropic therapy, wobenzym.

Introduction. Lyme disease (LD) belongs to “new infectious diseases” [2], which stimulant, spirochete of Borrelia burgdorferi sensulato complex, was discovered in 1982. In terms of incidence borreliosis takes a primary role among natural focal infections and presents one of the most important problems of modern infectious pathology, taking the leading position in terms of incidence and prevalence in most countries of Europe, Asia and USA. Thus in Europe level of LD incidence comprises 500 cases in 100 thousand of population [4], in USA – more than 90% from all diseases passed by arthropods, 12-14 thousands of incidents are registered every year.

The problem of berrelioses is relevant for the Ukraine too. Up to 1989 tick borreliosis was not systematically studied, though there were reasons to believe that natural foci can exist along the whole territory of the country [4]. Just in 1989 – 1998 natural foci and ailment of people with tick borreliosis were found in most regions of
the Ukraine during the research carried out by the Ukrainian centre of the state sanitary and epidemiological supervision and I.I. Shalgausen Zoology Institute of the Ukrainian NAS.

Study of natural borrelioses contamination and official registration of morbidity in the Ukraine is carried out since 2000, when 2 cases of LD incidence was registered which comprised 0.12 on 100 thousand of population, in 2016 – 169 (6.22 on 100 thousand of population). It can be explained both as the improvement of diagnostics and medical stuff and population awareness about this infection. It was stated that 57% of population have contacts with disease stimulants vectors which defines probability of population infection risk. Wide prevalence of LD and severity of clinical course stipulated for frequent transfer to relapsing and chronic forms attract attention of medical community to this infection, most typical among vector-born natural focal diseases of the Ukraine. In view that incidence of this infection is registered in all regions, yearly growth of it creates unfavorable epidemiologic situation in the country. The LD morbidity growth tendency is typical for Kharkov region [7].

The data of official statistics on LD morbidity in the region are presented in the table. But they are “the tip of the iceberg” and do not reflect the real level of morbidity, because the patients not always resort for help. Infecting by Borrelia does not cause abrupt changes in the general state of the patient. Such symptoms as ailment, body aches, amotivational weakness and even appearance of migrating erythema, which is a pathognomic manifestation of the disease, not always stimulate the patient to resort to the doctor. At the same time late diagnostics and late treatment stipulate for the appearance of relapsing and chronic forms and severe consequences of the disease can appear later up to invalidisation, though duly diagnostic and adequate antibiotic therapy do not guarantee organism rehabilitation [1]. It should be mentioned that at present antibiotics are prescribed in prolonged courses with maximal single dose in schemes of etiotropic therapy. In spite of this according to numerous data chronization of the infection occurs in patients from 3.5% to 10 - 13% depending on the preparation used [3]. Some specialists (L.E. Comstock et al., 1991; Y. Ma et al., 1991; M.S. Klemptner et al., 1992; P. Brougui et al., 1996) reasonably consider that intracellular presence of Borrelia especially in cases of stimulant presence in remote for antibiotic organs and tissues (cerebrospinal system, cerebral tissue, joints), as well as the ability to infest fibroblasts and endothelial cells which essentially complicates etiotropic therapy, stipulates for durable persistence of Borrelia in organism.
All this in complex forces finding new ways of efficacy of etiotropic therapy improvement in LD treatment.

Lately for the improvement of infection diseases treatment results complex therapy including system enzyme therapy (SET) is particularly used. It is well known that natural enzymes (polyferments) of vegetable and animal origin being the component part of wobenzym have a number of important curative properties, in particular, anti-inflammatory, immune modulating, anti-edema, analgesic and fibrinolytic activity, potentiating antibiotics activity, decreasing their toxicity and frequency of side effects. In this connection SET is an important component of booster-therapy («therapy of reinforcement») and service-therapy («therapy of insurance»). Under this therapy stimulant sensitivity to antibiotics increases, immunity and endogenic interferon production activate and vice-versa pathologic manifestations of autoimmune processes limit [2, 5].

The aim of our research was increase of treatment efficacy of patients with LD with the usage of complex SET.

Materials and methods. During epidemiological seasons of 2011 – 2016 years in the centre of diagnostics and treatment of the patients with borreliosis in clinics of the department of infectious diseases of Kharkov Medical Academy of Postgraduate Education on the basis of Kharkov regional clinical infectious hospital (RCIH) 246 patients at the age from 18 to 72 years old with the diagnosis “Lyme disease” were under supervision (144 women and 102 men were among them) with the diagnosis “Lyme disease”, average age comprised 46±12 years.

All the patients received complex clinical investigation accounting clinic-anamnesis data, epidemiologic anamneses, disease anamnesis, additional laboratory and instrumental investigation methods. The diagnosis was stated on the basis of epidemiological (fact of tick sucking), clinical (presence of erythema which is a pathognomic manifestation of the disease) and laboratory (detection by the method of IFA IgM and Ig G to Borreliaburgdorferis.l. in blood serum) data.

Antibiotics of wide activity spectrum of the following pharmacological groups: third generation cephalosporins, tetracyclines, macrolides were used for LD etiotropic treatment.

Inclusion in the study criteria were; LD, patients at the age from 18 to 70.
Exclusion criteria were the patients at the age of less than 18 years and more than 70, presence of chronic somatic pathology in anamnesis, taking of antibiotics before the therapy.

Depending on the results of the therapy all the patients were divided into two groups comparative according gender and age indications as well as schemes of therapy.

87 patients were included into the study group who along with standard ceftriaxone therapy (№ UA/6340/01/02 from 20.04.2012 to 20.04.2017, the producer CJS “Pharmaceutical firm “Darnitsa”. Kiev, Ukraine) got wobenzym in dose 1,0 g twice a day intramuscularly (3UA/2842/01/01 from 15/02/2010 to 15/02/2015, producer Mu-cisePharma Gmbch, Germany) 15 tablets a day in 3 takings for 14 days orally.

96 patients were included into the control group, they were prescribed only ceftriaxone therapy in the same dose and course. The groups were equal in gender and age indications.

Clinical study and examination of the patients were carried out in profile departments of RCIH, after discharge from the hospital – outpatient in consulting centre in diagnostics and treatment of Lyme-borreliosis patients on the basis of RCIH. The efficacy of the carried out therapy in LD patients was estimated in accordance with the Order of the Ukrainian HCM № 218 from 16.05.2005 “About strengthening of measures for the diagnosis and prevention of ixodid tick boreliosis”. The therapy was considered effective if under dispensary observation for 2 years no borrelia were detected either clinically or serologically.

Clinical data were estimated and classified in patients with LD (migrating erythema elimination terms, weakness, headache, presence of medications side effects, the illness outcomes, which were paid special attention on, etc.), laboratory indices (presence of specific Ig, interleukins level, CRE).

Statistic processing of the study results was carried out with the help of Microsoft Excel 2007 (Lic. № RW2FR-7DFDD-TCF8J-9K9BJ-MJ678) according to recommendations of statistic processing of medico-biological data. Arithmetic mean (M), average standard deviation (σ), medium error of arithmetic mean (m) were calculated for each variation series. The average meanings significance of differences estimation in comparative group (p) was carried out with the help of Student-Fisher criterion (t).
**Results and discussion.** Analyzing the data received it was stated that the period from tick bite to rash appearance vary from 1 to 20 days (often 7—10), which reliability depends on exactness of the fact of tick sucking ascertainment. At the same time according to literary data up to 30% of the patients did not remember or denied the bite of this vector in anamnesis.

The disease beginning was usually subacute with tiny painfulness, itch, swelling and redness in the place of tick sucking. The patients usually made complaints on tiny headache, moderate general weakness, ailment, feeling of contraction and sensitivity disorder in the area of tick bite. Objectively in 70% of patients a typical migrating loop skin erythema appeared in the place of tick sucking which was the main pathognomonic clinical indication of the disease – bright red color macula which gradually centrifugally spread. The centre of the spot gradually faded and periphery in the way of erythematous circle continued widening, reaching from 3 to 70 sm in diameter. Though, the severity of the disease was not connected with its size. In separate cases vesicle and tissue necrosis (primary affect) appeared in the place of initial lesion. Some red circles sometimes appeared with limits of external boundary. Skin symptoms were often accompanied by migrating pain in muscles and bones, arthralgia. In most cases (92%) syndrome of general intoxication was mindedly expressed. First symptoms of the disease usually weakened and completely disappeared in some days (weeks) even without treatment.

Increased pigmentation and skin peeling often remained on the place of former erythema. In 88% of cases the disease manifestations were limited by skin lesion in tick bite place and weakly expressed general symptoms. In 2 patients Borrelia spread hematogenously and lymphogenously on other areas of skin and then secondary erythemas appeared under which there was no primary affect in comparison with the main one.

Erythema was quite often accompanied by regional lymphadenitis (82% of patients), and seldom by lymphadenopathy. Lymph glands increased in size and were painful in palpation.

In 21% of patients with migrating erythema local pain syndrome took place in place of ixodes tick bite which can be one of the manifestations of periphery nervous system lesion: mialgiae, neuralgia, regional to the place of tick sucking. Numbness appeared in the place of disorder. Weakness of separate group of muscles and re-
flexes decrease appeared. Symptoms of inflammation were of unstable character and rather quickly disappeared after etiotropic treatment.

According to our observations body temperature was usually subfebrile and sometimes normal. Only in 3 patients in which anamnesis showed the tick bite in Carpathian region and Crimea in presence of erythema the body temperature increase was observed up to febrile numbers for 2-7 days.

Under non-erythemic forms the disease often manifested with typical symptoms for this stage of the disease with more severe course than in patients with erythemas. It is stipulated for absence of local inflammatory-allergic reactions in the way of migrating erythema and accordingly of quicker and more essential stimulant dissemination.

Indications pointing at possible meninges lesions appeared early when skin erythema still remained in 2 patients: headache, nausea, hyperesthesia, rigidity of occipital muscles. Thus they were not accompanied by syndrome of cerebrospinal fluid inflammatory changes. In one patient under examination and in 1/3 of the patients according to the literary data [6], the indications of moderate encephalopathy were found including sleeping disorders, concentration of attention and prominent emotional lability.

During some weeks from the moment of contamination indications of heart lesion appeared which had no characteristic features. Most often it was atrioventricular blockade (I or II degree, sometimes absolute), intraventricular violations of conductivity, rhythm violations. In some cases diffuse heart lesions developed including mio- and pericarditis, dilatational myocardiopathy and pancarditis.

Lesion of junctions of borrelious etiology hesitates from 2 to 10% depending on geographic region. Their involving into pathological process was mostly met in non-erythemal form and was characterized by intermitting and migrating reactive arthritis manifestations, accompanied by painfulness, hyperemia, possible swelling. Usually big junctions of the finiteness where tick sucking was found were involved into the process which proved about local spreading of Borrelia from initial focus in skin. Under repeated aggravations other junctions and periarticular tissues were involved into the process which was accompanied by pain in bones, muscles, ligaments. Arthritis took chronic, continuous or relapsing course without etiotropic treatment. In biopsy of synovial membrane fibrin deposits, villus hypertrophy, vessels proliferation and exposed plasmocytic and lymphocytic infiltration were found.
One of B.burgdorferisensulato dissemination manifestations was liver lesion later called Lyme hepatitis. Indications of its lesion included heaviness in right hypochondrium, light diarrhea disorders, moderate liver enlargement and often moderate changes of functional samples. Thus, increase of AST level was registered in 6% of patients, ALT – in 19%, bilirubin – in 3%.

Late violations of the nervous system were manifested by chronic encephalomyelitis, spastic paraparesis, ataxia, obliterated memory violations, chronic axonal radiculopathy. Polyneuropathy with radicular pains and distal paresthesias was observed. Patients demonstrated headache, increased fatigue, hearing worsening. Skin lesions were manifested in the way of acrodermatitis and sclerodermatous changes.

The first stage of early localized infection was diagnosed in 59,5 % of patients, the second – stimulant dissemination - in 25,3 % and the third– persisting infection – in 15,2% of patients.

Unfortunately, at present it is difficult enough the define Borrelia sensitivity to antibiotic in connection with difficulties in stimulant isolation, especially in cases of the disease chronic course. The schemes of etiotropic therapy with the aim of LD treatment are at present prescribed, as it was mentioned, in prolonged courses with maximal single doses. In prescription of etiotropic therapy to the patients the choice of antibiotic was based not only on pharmacokinetic properties of the preparation but also on the stage of organic violations, duration of the disease, clinical form, state of the patient, his premorbid background. In this case it is always important to take into consideration that disappearance of the disease clinical manifestations not always demonstrate the recovery with complete elimination of the stimulant because, taking into account the peculiarities of LD course, absence of clinical indications after the therapy does not jet testify about the termination of infection process.

Monotherapy by the mentioned above antibacterial preparations in our observation was effective in 71,9%, while 21,1% of the patients resorted for medical help iteratively in connection with complaints appearance stipulated for transition of the disease into the next, relapsing stage. Moreover, in 9,1% of cases relapse appeared after adequate treatment, and in 19% – it was stipulated for insufficient dose or terms of treatment. Thus, the nervous system both central and periphery, skin, cardiovascular system, joints were involved into this process. It is necessary to mention that the symptoms and syndromes mentioned above were both isolated and blended
in various combinations. Thus in particular in the patient with chronic atrophic acrodermatitis myocarditis was diagnosed.

The presented results of etiotropic treatment demonstrated that antibiotics prescription even in sufficiently continuous course does not always define the expected favorable outcome (relapses appear and then chronic forms). In this connection wobenzym was used in complex therapy. 87 patients comprised an experimental group who took wobenzym in dose 20 pills a day in 4 intakes for 14 days inside together with standard ceftriaxone therapy in 1,0 g twice a day intramuscularly. Control group comprised 96 patients with LD who were prescribed therapy of only ceftriaxone in the same dose and in the same course. The groups were equivalent according to gender and age indications.

The following main criteria were included for definition of suggested schemes of therapy efficacy: terms of migrating erythema elimination, duration of general intoxication syndrome, presence of medications side effect, disease outcomes, which were paid special attention to.

The carried out research demonstrated that tick erythema in the patients of the experimental group in most cases disappeared on the 4-5th day after treatment (in average – on the 5,1 day), in patients of the control group – on the 8th day and later (maximum up to 17 days from the beginning of the treatment).

Comparing the terms of subjective symptoms of tick erythema disappearance – pain and itch – it can be noticed that these symptoms disappeared in all patients of the experimental group on the 3-4th day from the beginning of the treatment while in control group – on the 6th day.

Side effect of medications was observed in patients treated by ceftriaxone (4 cases) which was taken into account during treatment. The appeared diarrhea features were manifested by nausea, burden in epigastrium, worsening of appetite. One patient demonstrated allergic reaction on the 3-rd day of the treatment which was characterized by skin itch and urticamea exanthema on the belly which were docked by Claritin. In parallel group side effects were not observed which was probably connected with wobenzym taking which neutralized side effects of antibiotics.

Thus highly reliable therapeutic effect was found on each of analyzed symptoms being apparent in the way of their manifestations term shortening in the research group.
Under complex estimation of average duration of all symptoms in the groups it was stated that in general the disease clinical manifestations leveling in the research group (1.98 ± 0.14 days) was carried out in 2.2 times quicker than in comparison group (4.4 ± 0.29 days, p<0.001), which proves the efficacy of combined therapy.

Analyzing the data received it should be mentioned that significant differences were found in groups only in IL-4. Thus part of the patients with relatively low content of cytokine (≤70.0 пкг/мл) in the research group (41.7%) was defined in 4.1 times more frequent than in control group (9.1%, p<0.05), as well as in the patients of this group a tendency to lower meanings in other indices was found. Besides a tendency to growth of part of the patients with specific Ig G antibodies in the research group (83.3%) in comparison with control group (72.2%, p>0.05) was found.

The received data prove that in contrast to clinical semiology immunological indices have greater haste concerning their normalization, which does not allow the effect of combined therapy fully reveal. Though if the number of patients with immunological indices close to normal was summed up and their specific weight in each group was defined the part of such patients in the research group comprised 54.2% and in control group it was reliably lower – 30% (p<0.01). It follows that the tendencies of more prominent effect of complex therapy on immunological homeostasis normalization reveal addictive effect, defining in general reliably more essential treatment efficacy with the usage of wobenzym in comparison with the control group.

**Conclusion.** Resuming the mentioned above it is important to underline that the carried out research revealed that LD course depending on the stage in our investigations did not practically differ from the one described in literature. The treatment results appeared reliably better in patients who received wobenzym in complex therapy: recovery was marked in 92.5% of cases, in comparison group its number was 87.9%. Relapsing and chronic course in most cases was met in patients whose etiotropic treatment excluded wobenzym. Complex therapy caused more prominent effect, in comparison with monotherapy, directed on the disease clinical manifestations elimination which confirms synergy of antibiotics with SET preparations. Besides in combined therapy prescription a tendency to more prominent than under monotherapy dynamics of immunological indices meanings to their normalization was marked. The reached therapeutical effect allows recommending the usage of SET in LD treatment.
References: