Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Friedrich Schardt and Bernd Schmausser, 2023. Different Treatments in Patients with Neuroborreliosis and Coinfections. Medical Research Archives, [online] 11(9). https://doi.org/10.18103/mra.v11i9.4488

DOI: https://doi.org/10.18103/mra.v11i9.4488

ISSN: 2375-1924

RESEARCH ARTICLE

Different Treatments in Patients with Neuroborreliosis and Coinfections

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ABSTRACT

In case of an acute infection of borreliosis, the best therapy is azithromycin 500 mg combined with cotrimoxazole 960 mg, 2x1 per day mostly over 10 days. For chronic and long-lasting infections rifampicin 450mg can be added. There is also a coinfection with babesia atovaquone combined with tinidazole that should be subsequently followed. In a long-lasting stadium of a neuroborreliosis with typical symptoms mostly combined with other bacterial and viral coinfections hydroxychloroquine and/or disulfiram are the best therapy. Whereas disulfiram inhibits P 450-cytochrome, fluconazole induces this elimination system so a combination with artemether is useful. Disulfiram penetrates all tissues, but also cytoplasm, nucleus, and mitochondria, and passes the blood-brain barrier. Cystic borrelia has a low and downregulated metabolism for a long period, you need a long time (about 18-21 months) to block the mechanism for energy supply (ATP) and replication. Homeopathic dispensing and plant extractions as well gamma-globulins are surely effective during chronic or relapse stadium.

Introduction

Neuroborreliosis is a tick-borne infection of the nervous system transmitted by several species of borrelia in the stadium II or III of a borreliosis. The neurological manifestations were first described in 1922 in a patient with meningo-radiculitis after a tick bite with following erythema migrants[1]. This is based on special attributes of these gram-negative bacteria which can actively move also by blood or in the lymphatic system and reach all organs and tissues of the body. The preferred tissues for borrelia and their cystic forms are fascia, CNS, liquor, tendons, and synovia[2].

Borrelia burgdorferi consists of one large linear chromosome that is 910 725 base pair long. This chromosome contains approximately 853 genes coding for basic functions such as DNA replication, transcription, translation as well transport, and metabolic systems. Additionally, it has 17 linear and circular plasmids with 533,000 base regulations. Research has shown that virulence depends on the number of plasmids because they may encode virulent DNA[2].

By this, a wide range of symptoms with different severities is included such as aseptic meningitis cranial or spinal discitis, acute myelitis, cerebral vasculitis, chronic progressive encephalomyelitis, acrodermatitis chronical atrophicans, and polyneuritis[3]. The results of several investigations show that the borrelia adapts different strategies for its survival inside the immuno- competent lost from the time of infection until migration and dissemination in different parts of body tissues. The success depends on its ability to colonize the host's immune defence mechanisms. During this process, the spirochete seems to maintain its vitality to ensure long-term survival in the host[4]. Borrelia's proteins are encoded by plasmid and chromosomal genes. These genes are differentially regulated and expressed by different environmental factors in ticks as well as in the mammalian host during infection. Moreover, antigenic diversity enables the borrelia to escape host defence mechanisms and main infection[5,6]. Especially combined with viral (i.e. EBV, SARS, CMV, FSME) and bacterial coinfections (i.e. Bartonella, Chlamydia) or immunosuppressive therapy the antibody level is reduced (CD57, NK-cells). Additionally, borrelia develops in tendons, fascia, and nerve tissues cystic forms are unreachable for antibiotics and immunological response and can revive to active forms[6]. To these attributes, the patients complain of relapses of migrating pains and different signs of paralysis[7]. Research has shown that virulence depends on the number of plasmids because they may encode virulent DNA[2,3].

As a consequence of these special characteristics regarding genetic abilities and migration, borrelia causes some difficulties in diagnosis and therapy. The abilities of borrelia:

- long term multiplication (18–24 hours)[3]
- Intracellular persistence[6]
- Cystic and round form for survival in the tick and human body.[6]
- immune suppression by toxins[7]
- migration and evasion[8]
- Antigen shift at the external membrane[7,9,10]
- Generally, they have a special preference for synovial tissue, the central nervous system, and liquor according to their metabolism.
- Based on these special abilities of borrelia the medicaments against neuroborreliosis have to fulfil the conditions:
- It has to be effective extra and intracellular.
- effective also in cystic forms and round bodies and a high CNS/ liquor concentration[11]

The problem is that the effective antibiotics cephalosporins, macrolides, and tetracyclines have no effect on cystic forms. Therefore, only a combination of antibiotics with antimalarial drugs or co-drugs as artemether, metronidazole or tinidazole, and hydroxychloroquine show all abilities regarding intracellular existence, on cystic form and liquor concentration. According to the bioavailability of the antibiotics two different antibiotics and co-drugs were always simultaneously sequentially combined together with antimalaria drugs. The goal of this study was to analyze effective therapies against borrelia and to investigate the coinfection of borreliosis[12].

Especially in the chronical stadium of neuroborreliosis, a liquor punction shows indeed some typical changes. But because there are

mostly no lymphocytes by the limiting haematoencephalic barrier there is no diagnostic profit in comparison to the risk of an invasive method. For the chronic phase (migrating pain in skin, tendons, muscles, and joints) the main focus of efficacy is the central nervous system. Therefore, fluconazole was chosen because it is the only derivative of the azoles which is reaching together with hydroxychloroquine a high concentration in all tissues and liquor[13]. Therefore, as a basic principle, an effective antibiotic should be always combined with a substance of the group of co-drugs. An example of possible combinations is shown in Table 1.

Table 1 Antibiotics and Co-Drugs fulfilling therapy conditions against borrelia combined with their pharmacological characteristics.

Antibiotics	Intracellular effective	CNS effective	Cerebrospinal fluid concentration	Cystic forms effective	Half-value time
Roxithromycin	+	+	?	-	10 - 12h
Azithromycin	+	+	?	-	30h
Co-trimoxazol	+	-	?	+	12h
Cefuroxim	+	-	-	-	15h
Ceftriaxon	+	-	-	-	8h
Cefotaxim	+	+	-	-	1h
Doxycyclin (bacteriostatic)	+	14%	-	-	15h
Minocyclin (bacteriostatic)	+	?	40 %	-	18 - 20h
Co-Drugs					
Tinidazole	+	+	+	+	10h
Hydroxychloroquine	+	+	+	+	30 days
Artemether	+	+	+	+	4h
Fluconazole	+	+	+	?	24h
Disulfiram	+	+	+	+	8h

If joint pains intensify during treatment with fluconazole, fluconazole therapy should be limited to 20 days and the entire treatment should start from the beginning.

All stages of Lyme disease (borreliosis) must be treated with antibiotics therapy, including stage I, erythema migrants. Only a rigorous adherence to the therapy can prevent the development of neuroborreliosis. Bactericidal antibiotics (penicillin, cephalosporins, macrolide) generally are more effective than doxycycline. Doxycycline should not be the first choice of antibiotics because it only acts as bacteriostatic (preventing the growths and multiplication of borreliosis). Moreover, the bioavailability of minocycline in the tissues is better and works against Ehrlichia, Babesia, and Bartonella. Despite all these applied therapies relapses are often observed. Regarding the numerous publications in international scientific journals, the objective and goal of this meta-analysis and review was to report on own experiences with different treatments in patients with neuroborreliosis and coinfections.

Material and Methods

Only patients with a certified diagnosis based on the following conditions of symptoms and serological tests were included in this study.

The diagnosis of neuroborreliosis is determined utilizing the following criteria.

- Positive ELISA and Western blot (IgG, IgM), LTT, and Immunofluorescence test (IFT)[14]
- Typical symptoms, such as unspecified, wandering nerve pain (especially at night), alternating paralysis in the lower extremities, depression, forgetfulness, and panic attacks[15].

These must correspond with the questionnaire filled out and signed by the patients which was subdivided into:

- Anamnesis
- Common complaints
- Disorders of CNS and peripheral nerves
- Eye illnesses
- Pains of joints and muscle disorders
- Digestion disorders
- Heart and circulation diseases
- CNE disorders
- Endocrinological disorders
- Skin diseases
- Different complaints

Other possible causes for these symptoms had been eliminated through laboratory tests (blood tests) and MRI.

Since fluconazole does not appear to eliminate borrelia from the central nervous system but instead prevents their growth and reproduction, the therapy must be continued for at least 20-50 days to be effective. If after that period symptoms persist, the therapy (antibiotics, followed by fluconazole) can be repeated consecutively up to three times. If these criteria had been fulfilled 923 patients (497 female, 426 male) entered the study (2005-2020) to test the success of the therapy schemes.

All patients of our study had been serologically tested together with Borrelia (IFT, ELISA, Western blot, IgG, IgM) in Babesia, Bartonella, Chlamydia, Toxoplasma, Ehrlichia, Anaplasma, Rickettsia, Tularämia[16] Mycoplasma, Syphilis (IgG, IgM), Herpes-, Parvo-, Borna-, Coxsackie, Covid 19 and EB-Virus (IgG, IgM)[17]

In the chronical stadium of neuroborreliosis, there is mostly no liquor punction necessary. It shows indeed some typical changes but because there are mostly no lymphocytes due to the limiting blood-brain barrier, especially in comparison to the risk of an invasive method.

Results

In 27,8%, a positive borreliosis serology and typical symptoms were connected with one, 39,1% with two, and 33,1% with three coinfections. The coincidence with detailed coinfections shows the following list 1.

List 1 In all cases Borreliosis related to.

• 98,7% EBV • 71,4% Herpes-Virus • 34,9% Toxoplasma • 31,4% Bartonella • 25,1% Chlamydia • 24,2% Borna-Virus • 21,3,2% Babesiosis • 17,9 Coxsackie-Virus • 17,3% Parvo-Virus	• 14,9% Mycoplasma • 10,4% Anaplasma • 10,2% Rickettsia • 9,7% Ehrlichia • 9,6% COVID-19 • 7,3% Parvo-Virus • 0,5% Syphilis • 0,2% Tularämie

Because of multiple coinfections, the addition of all with borreliosis-connected infections was more than 100%. At the end of the antibiotic therapy and exactly two years after the end of the therapy all patients got a questionnaire about success and still existing complaints. However, only 238 questionnaires were returned. In Table 2 all successes and relapses are recorded.

Table 2, Success after antibiotic therapies and relapses with complaints after 2 years

CNS- complaints after antibiotic therapies		
heavy	moderate	light
6,1%	32,4%	61,5%

Joint and muscle complaints after 2 years		
heavy	moderate	light
13,5%	38,1%	48,4%
Migrating peripheral pains and complaints after 2 years		
heavy	moderate	light
13,0%	36,3%	50,7%

Table 3

Relapses after 2 years predominantly (n=238)		
CNS-complaints	joint and muscle complaints	migrating peripheral complaints
29,3%	46,5%	24,2%

Discussion

It is well-known that children with an excellent immune system overcome very well a borrelia infection sometimes supported by a penicillin-antibiotic. According to the valid guidelines, doxycycline is the first medicament applied for acute infection and erythema migrants. But based on the data of bioavailability the concentration of CNS and liquor are too low. Furthermore, it has no efficacy on cystic forms of borrelia, so relapses mostly occur. Minocycline is a little better with its data for bioavailability, but the characteristics are comparable. Especially in an acute stadium ceftriaxone and cefotaxime per infusion are excellent antibiotics. They have a good bioavailability in CNS but not so good in liquor. Under special considerations of pharmacological capacities in the preferred tissues of borrelia and their sensibility to antibiotics and co-drugs, only a few remained. This is caused by many special abilities of borrelia based on the interacting functions of its genes and plasmids. Borrelia produces two types of toxins: endotoxin which is a non-secreted lipopolysaccharide as already mentioned and obviously also an exotoxin, a so-called lipophile neurotoxin which is still discussed.

The antigen shift at the outer membrane is surely caused by its large number of different lipoproteins which are encoded by exceptionally fragmented and predominantly linear genome. The research data indicated till now 125 analyzed lipoproteins and the remaining 39 periplasmic leaflets in the inner membrane. By these specialties, borrelia is unique among diderm bacteria in abundance of surface-displayed lipoproteins which play an important role in immune deficiency and relapsing fever[18]. These periplasmatic lipoproteins with a steadily increasing number of different constellations are encoded mainly by plasmids contributing to the host-pathogen interface[19]. Moreover, damages

or reduction and suppression of the energy production in human mitochondria were also discussed as caused by lipophile toxins produced by borrelia or their decay[20]. This could be the reason for migrating pains revealed by radicals or low energy levels in the mitochondrial metabolism. The same mechanism will be released obviously by a lipophile neurotoxin compensated by cholestyramine. This corresponds with the observation of many patients that cholestyramine works like an antidot against this neurotoxin for the time of therapy.

Additionally, borrelia develops complement evasion mechanisms of microbial pathogens for selective C 1 inhibition and antibody-mediated complement activation. These different facilities of borrelia are based on the complex genome and a high number of plasmids present a special problem in Lyme disease and therapy[21].

The results of our study present a very high incidence and connection with EBV infection higher than the normal incidence and prevalence in the normal population is. The Epstein-Barr-virus (EBV), a double-stranded DNA virus, is one of the most common viruses in humans (about 90%). Mostly EBV infects B-cells of the immune system and epithelial cells. When EBV infection is brought under control, the virus persists in the individual`s B-cells for the rest of life predominantly in bone marrow[22,23,24]. Tight connection is very often an autoimmune disease and immune deficiency[25]. Therefore, the preparation effect for chronic neuroborreliosis is considerable. Azithromycin is a proven antibiotic against borrelia and has excellent bioavailability in all tissues, especially in CNS[26]. The same attributes are valid for cotrimoxazole. That is also the reason for combined therapy.[12]

Rifampicin is almost used together with other antibiotics because it works by decreasing the production of RNA by bacteria and stimulating cytochrome P 450. It is also recommended as an alternative treatment for infections by tick-borne pathogens: Borrelia burgdorferi and Anaplasma phagocytophilum.[16,27] Besides the ability for intracellular persistence in cystic forms and antigen shifts at the external membrane borrelia can form biofilms which an important role in their survival in diverse environmental conditions by providing refuges to individual cells. Rifampicin can penetrate these barriers by its chemical structure and to work as an antibiotic[11].

The nitroimidazoles such as metronidazole or better tinidazole are very effective members in the treatment against borrelia and bacterial coinfections[11]. If babesia are also positive atovaquone should be applied because they are sometimes transmitted by ticks, too. The combination with azithromycin works especially effectively.[28]

Fluconazole is normally used for a number of fungal infections and inhibits the fungal cytochrome P450 enzyme. Moreover, with excellent bioavailability in the brain and liquor, it is very qualified for all tick-borne bacterial infections. Since fluconazole does not appear to eliminate borrelia from the central nervous system but instead prevents their growth and reproduction, the therapy must be continued for at least 20-50 days to be effective. If after that period symptoms persist, the therapy (antibiotics, followed by fluconazole) can be repeated consecutively up to twice.[13,29]

Hydroxychloroquine has a wide therapeutic effect in the treatment of post-Lyme arthritis and Sjögren syndrome. Its pharmacological efficacy is further unclear. It may have an anti-spirochete and antirheumatic activity.[30] Hydroxychloroquine is according to its chemical structure able to pass lipid cell membranes and concentrate in cytoplasmatic vesicles. A high pH within lysosomes causes decreased intracellular processing, glycosylation, and secretion of proteins with many immunologic and nonimmunologic consequences.[31,32] Hydroxychloroquine and its metabolites have inhibitory effects on cytochrome P 450 and nine different subtypes, especially in microsomes of the human liver[33].

Artemether is an extract of mugwort and is normally used for the treatment of uncomplicated malaria and for preventing schistosomiasis. Its mechanism is inflicting metabolic and oxidative stress on borrelia in relation to glutathione and glucose metabolism with the consequence of lesions and reduced growth. Therefore, it could be an effective supplement to disulfiram.[34] The absorption is improved 2-3-fold with food, and it is highly bound to protein artemeter combined with

lumefantrine and should not be used with drugs that inhibit cytochromes[35,36]. Whereas diverse antibiotics and co-drugs can be brought effectively into action with bacteria against viral infections (i.e. EBV, Borna, Herpes, West Nile, Dengue, Coxsackie, Parvo) only gamma-globulins and immunostimulants are causal in use[35]. For a bornavirus infection especially amantadine is recommended.[38,39]

Disulfiram is normally used to support the treatment of chronic alcoholism by producing an acute sensitivity to ethanol[40]. Whereas the first step catalyzed by alcohol dehydrogenase takes place in the cytoplasm, the second step by aldehyde dehydrogenase is localized in mitochondria. Disulfiram is well absorbed, fat-soluble, and eradicates all forms borrelia can take. It penetrates all tissues, but also cytoplasm, nucleus, and mitochondria, and passes the blood-brain barrier[41]. The effect is probably because the four sulfur atoms in the center are shaped into a ring (chelate) which contains Zn++, Cu++, and Mn++. All unicellular organisms need these cations as central atoms for the activity of enzymes in mitochondria i.e. (superoxide dismutase: Mn++, LDH: Cu++, ALDH2: Zn++). This blocks the mechanism for energy supply (ATP) and replication which ultimately leads to the death of these microorganisms and is obviously the reason that low dosages work selectively on microorganisms[42]. Recent experiences with disulfiram showed efficacy in a dosage of 100-200 mg/day against Bartonella, malaria, babesia, and different viruses over several weeks[43]. The mechanisms of action to these germs is nevertheless still unclear. A clinical study on 229 chronic Lyme patients with coinfections have become asymptomatic not before 18-21 months. Relapses of Lyme-disease under disulfiram are obviously possible because some persistent forms of borrelia are able of downregulating metabolism and vital cell processes and escape by this way the efficiency of disulfiram. An interval therapy or an interruption of the therapy with disulfiram is therefore possible.

The effects of phytochemicals, homeopathic drugs, and antimicrobial agents of plants herbs, and spices like stevia colchicum, cat`s craw, artemisia, rhus tox, Argentum metallic, Andrographis et cetera are not secure[44]. In acute infection, antibiotics combined with co-drugs and antimalaria medicaments, and for chronic stadiums plant and disulfiram are the approved therapy. Finally, the importance of having borreliosis combined with any kind of coinfections (virus, bacteria) is the interaction and suppression of the immune system by coinfections.

Conclusions

In acute infections of borreliosis characterized by strong pains in muscles and joints combined mostly with fever antibiotics especially azithromycin and cotrimoxazole with co-drugs should be applied. For chronic stadiums like neuroborreliosis and relapses homeopathic and plant drugs as well disulfiram can be used.

Acknowledgment

We thank Mr. Maximilian Schardt for text processing and configuration of tables und lists. All authors read the reviewed manuscript. The authors declare that they have no conflict of interests. The ethical standards and procedures for research with human beings are fulfilled.

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