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OUR CLINICAL EXPERIENCE CONCERNING PATIENTS DIAGNOSED OR SUSPECTED OF *BORRELIOSIS*/LYME DISEASE

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Introduction: This article presents some main aspects of our clinical expertise regarding *Borreliosis*/ Lyme disease.
Objectives: Clinical, laboratory and therapeutic evaluation of patients diagnosed or suspected of Borreliosis, hospitalized or ambulatory visited in the Neuro-Rehabilitation Clinic Division of TEHBA, in a retrospective study (Annex – Commission ethics approval).
Material and methods: We have studied a small but consistent with the prevalence of the disease, lot of 11 patients: 7 inpatients at our above mentioned clinic division and 4 outpatients, during June 2008 and May 2013. Their evaluation was based on epidemiological data, clinical signs, para-clinical items (serological, respectively Dark Field Microscopy, confirmation and also blood cells count and erythrocytes indices such as MCHC, MCV, ESR, respectively: fibrinogenemia, glycaemia, lipemia, serum urea and creatinine – dynamically investigated), and based on the measurement of the respective parameters' pre- and post-therapeutic variation, we have evaluated the responsivity to the specific treatment (only possible for the ESR – see further). We used methods of descriptive statistics and distribution of parameters graphically expressed and also the "Wilcoxon signed rank" test to assess the ESR values variation.
Results: The majority of the studied patients were mid-aged, women, with urban residence and with specific serologic tests positive; most of the symptoms and signs (from anamnesis and/or clinic findings) encountered by them were: neurologic, followed by ocular, articular and psychiatric, and respectively, cardio-vascular manifestations; regarding neuro-imagery 46% of the investigated patients had demyelinating lesions. As for the treatment, the large majority (82%) of our subjects received appropriate antibiotherapy, including with ceftriaxone.
According to the Wilcoxon Signed Rank test, despite ties for two patients, the antibiotherapy produced statistically significant decrease of ESR values ($p = 0.042$).
Concerning the variation "before" and "after" treatment of the eosinophilia's values, considering the resulting $p = 0.5$ this places such an outcome in statistical "absolute ambivalence".
Other above mentioned investigated parameters showed no significant changes and respectively, fibrinogenemia, glycaemia, triglyceridemia, leucocytes, neutrophils and MCHC, emphasized p values rather suggestive for lack of change between "before" and "after".
As regards the main clinical symptoms' pre-/post therapeutic dynamics, the small number of cases prevented rigorous, valid statistical assessments; however, we detected worsening in none of them.
Discussion and conclusions: Antibiotic therapy applied in *Borreliosis*/Lyme disease had, as positive aspects, the lowering of ESR and respectively, also a possible – but completely doubtful – negative one: the equivoque afore mentioned variation of eosinophilia's values.
Hence, more precise and earlier diagnosis of this disease is both, a complicated but so necessary endeavor: better results can be obtained if the appropriate treatment is promptly given to the patients – also avoiding, thus, multiple and very prolonged antibiotherapy, especially if it isn't necessary – this last aspect representing, itself, a medical and socio-economic goal.

Keywords: *Borreliosis*, Lyme disease, neuro-borreliosis, antibiotherapy.

INTRODUCTION

A complex disease that implies an interdisciplinary team formed by: infectionists, rheumatologists, neurologists, rehabilitation doctors, cardiologists, ophthalmologists, dermatologists and also general medicine doctors for its strengthen monitoring[1], is considered to be *Borreliosis* or Lyme disease/illness (also known as Lyme arthritis[2]).

This is a tick-borne illness named after the Old Lyme town from Connecticut district, U.S.A (where the Lyme arthritis appeared and was reported for the first time in children, in 1975[3–6]) produced by Borrelia burgdorferi spirochetes and transmitted by ticks of the genus Ixodes[7–12] through vectors such as reptiles, birds, mammals[9,10,12] as already mentioned in a previous article of ours[13].

From etiological point of view, an important role in the occurrence of Lyme disease can be attributed to *Borrelia sensu stricto* – also called *Borrelia Burgdorferi* (after Willy Burgdorfer who first isolated this spirochete in 1982[14]) – predominant in North America, but also present in Europe (probably through migratory birds[6]); other Borrelia subspecies that are: *Borrelia afzelii*, and *Borrelia garinii* (predominant in Eur-Asia)[15] and the illness complexity can be explained by successive or simultaneous infections with different geno-species (there are more than 300 types of this bacteria discovered worldwide)[16].

The incidence of the disease even if it is not yet considered to be endemic it is estimated to be around 100.000 cases in USA[17] and 11.951 in Canada; in Romania are around 8200 patients with Borreliosis[17].

Borreliosis is considered to be "the disease with 1000 faces"[18] because of its clinical polymorphic characteristics that can mimic manifestations of an important number of illnesses[19].

During dissemination via circulation, the spirochetes can be isolated in blood/cortico-spinal-fluid (CSF), which correlates with the appearance of symptomatology: enlarged lymphatic nodes/ mononucleosis-like, neurological, articular, cardiac – all mostly immuno-inflammatory mediated. Eventually the infection may spread progressively in different tissues with strong tendency to cronicisation rather frequently being located in the synovial fluid but also possibly in vital on such as of the heart[20].

Borreliosis, because of its various targeted structures in the body – and consequently being difficult to be diagnosed – can remain uncertain for long periods of time.

The main manifestations of this illness that can determine major sequels are the neurologic, arthritic, cardiologic and ophthalmologic ones, all with marked potential to generate an invalidating condition/ important disabilities[1]. The clinical symptoms are detailed in a previous article of ours[13] and considering the specific of our clinic division we herein focus on arthritics and neuro-borreliosis symptoms.

The muscle-skeletal affects (enthesitis, cellulites – mono/oligo articular – arthritis and an particular form: remitting seronegative symmetrical synovitis with pitting edema "RS3PE" syndrome[2]) are generally of short duration (7–10 days)[1,6]. The common symptoms in such cases are migratory arthralgia – possible arthritis – which if not treated[4] (rarely) can complicate with myositis[21] and even osteomyelitis[22].

We herein, below present briefly, some images within our expertise on articular clinical modifications.

Figure 1

Figure 2

Figure 3

Figure 4

Figures 1–4. Articular manifestations of Lyme disease (from the archive of Neural-Muscular Rehabilitation Clinic Division of TEHBA).

Specifically, from our casuistry, we synthetically present below two cases of borreliosis with neurological symptoms and MRI objectified lesions.

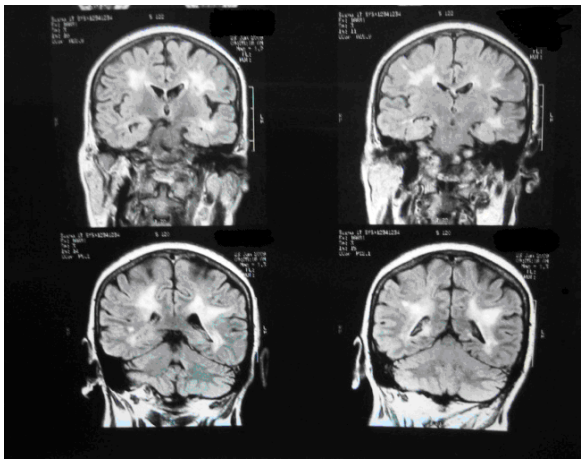


Figure 5

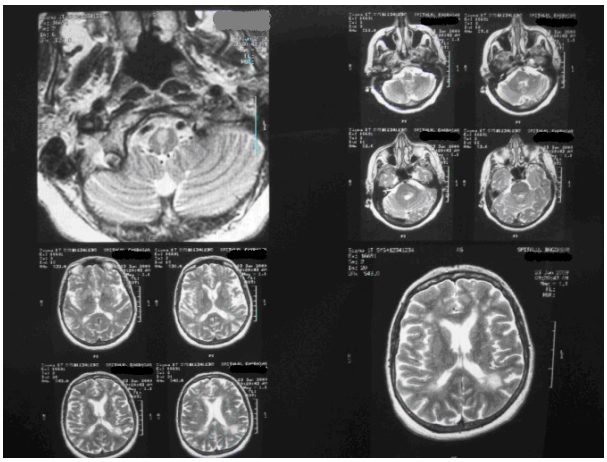


Figure 6

Figures 5, 6. Neuro-borreliosis brain injuries (from the archive of Neural-Muscular Rehabilitation Clinic Division of TEHBA).

"Lyme neuroborreliosis (LNB) is an infectious disorder of the nervous system" caused by the mentioned spirochetes[23] and has as common symptoms: ataxia, sleep and/or memory disorders – more common for subacute encephalopathy, but sometimes resembling to a leukomyelopathy – injuries of cranial nerves, spastic paraparesis, neurogenic bladder, radicular pain[23] and psychiatric manifestations[24].

The paraclinical evaluation through MRI/ CT of the related lesions may reveal the brain injuries induced by Borrelia: cerebellar atrophy, possible – but not exclusively – nonspecific demyelinating lesions including at medulla oblongata level and/or formation of inflammatory areas/vasculitis etc.[4]

A female patient, 54 years old, with diagnosis of: mild ataxic paraparesis with crural pain and paraesthesia on the right side with chronic neuro-borreliosis like background; the cerebral MRI shows: "multiple areas of hypo signal of T2 and FLAIR obvious at the supra- and infra-tentorial levels, including with the medulla oblongata. The aspect is of demyelinating lesions, more evidenced periventricular".

A female patient, 63 years old, with diagnosis of: ataxic and dysarthric syndrome, on the background of chronic reactivated neuro-borreliosis shows on the cerebral MRI – "multiple lesions HT2 and FLAIR with iso-signal in diffusion, with dimensions up to 1 cm located in the periventricular

white matter fronto-parietal bilaterally and subcortical frontal inferior right; slight demyelination of the periventricular white matter. Conclusions: unspecific demyelinating lesions with the described topography. Leukoaraiosis".

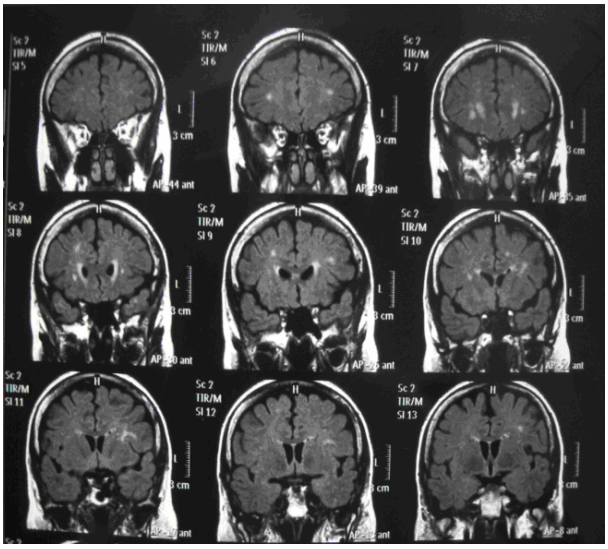


Figure 7

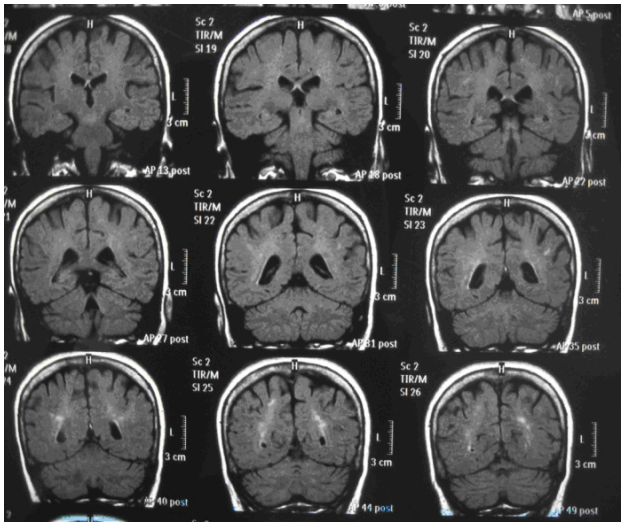


Figure 8

Figures 7, 8. Cerebral lesions in neuro-borreliosis (from archive Neural-Muscular Rehabilitation Clinic Division of TEHBA).

The paraclinical evaluation through cultures of Borrelia burgdorferi from: skin lesions, synovial fluid, blood, CSF and serological tests of: immunofluorescence/ immunoassay (antibody determination), ELISA, Westernblot, Polymerase Chain Reaction (PCR)[3] are only used for confirmation/ exclusion of the infection because the diagnosis (still a scientific debating problem) is based primarily on clinical manifestation and epidemiological data.

The pharmacological treatment is focused on an appropriate antibiotherapy associated with all supportive/symptomatic medication, when needed, but there is no unanimously accepted schema, only various therapeutic options.

STUDY DESIGN. OBJECTIVES

We made, in a retrospective study, clinical, laboratory and therapeutic evaluation of patients diagnosed or suspected with borreliosis, hospitalized or ambulatory visited in the NeuroRehabilitation Clinic Division of TEHBA. For a rigorous study unrolling, we have obtained the TEHBA Ethics Commission approval, too (Annex 1).

MATERIALS AND METHODS

We have studied a small but significant[1] lot of 11 such patients, during June 2008 and May 2013. Their evaluation was based on epidemiological data, clinical signs, para-clinic items (serological and Dark Field Microscopy tests of confirmation, and also blood cells count and erythrocytes indices – such as MCHC and MCV –, ESR, fibrinogenemia, glycemia, lipemia, serum urea and creatinine – dynamically investigated) and based on the measurement of the respective parameters' pre- and post- therapeutic variation, we have evaluated the responsivity to the specific treatment. We used methods of descriptive statistics and distribution of parameters graphically expressed and also the "Wilcoxon signed rank" – statistic differentiation test available including for small volumes, used in order to objectify the (rather obvious) fact that ESR values decrease after antibiotherapy – with data processed in SPSS (www.spss.com/). For the

[1] In Romania there are almost 8200 patients with Lyme disease[25]; our country's population, in 2010, was 21.442.012 and the Lyme disease prevalence in Romania: 0,039%; to determinate the minimal number of cases necessary for acceptable validity of the statistical results it can be used the Taro Yamane formula: $n = N/(1+Ne^2)$ where[26,27]: n = minimal number of cases, necessary to be investigated; N = disease prevalence; e = error coefficient (0.1–0.5).

For Lyme-Borreliosis disease in Romania: $n = 0.0389$ for $e = 0.1$; it results that the minimal number to be investigated could be even 1 case (obviously the more cases analyzed the fewer risks of statistical validity limits of the outcomes).

descriptive part, there have been considered all the 11 patients included in the study; for the dynamics' evaluation we had available appropriate data only for 7 of these patients.

EVALUATION OF PATIENTS AND MONITORED PARAMETERS

Epidemiological data: age, gender, social, geographic area, method of admission.

Clinical data: neurological (paresis, disarthria, peripheral neuralgia/neuritis, ataxia, neurogenic bladder and/or bowel) ocular (visual impairment/s, papilary oedema), articular (arthritis, RS3PE oligoartralgia), psychiatric (depression, anxiety), cardio-vascular (fatigue, lipothimia/ dizziness).

Laboratory data: as previously mentioned.

RESULTS

Descriptive data: 64% of the studied patients were admitted in our clinic division and 36% were outpatients (Fig. 9), their mean age was 49 years (min = 23, max = 87, std.dev. = 18.788). The gender distribution was: 64% women, 36% men (Fig. 10); mostly urban: 64% *versus* 36% rural (Fig. 11); 36% living in plain areas and 64% in the hills regions (Fig. 12). From the 11 patients 82% were serologically confirmed (Fig. 13), 55% had DFM confirmation (Fig. 14), and respectively only 5 patients 45% had confirmation through both paraclinical methods. The main strains of Borrelia identified were: Burgdorferi, Afzelii and Garinii. (Figs. 15–18).

The main symptomatology types objectified were: (56%) neurologic – by far the most frequent, which was to be expected, considering the neurorehabilitative specific of our clinic division –, (17%) ocular, (11%) articular, (11%) psychiatric and (5%) cardio-vascular, ones (Figs. 19–21).

As already mentioned, from the 11 cases we have studied 7 were inpatients admitted in our clinic division and 4 outpatients visited, during June 2008 and May 2013.

The gender distribution shows that the majority of the studied patients were women (Fig. 10).

The majority (64%) of the studied patients had urban residence, 64% living in hill areas and 36% in plain zones (Figs. 11 and 12).

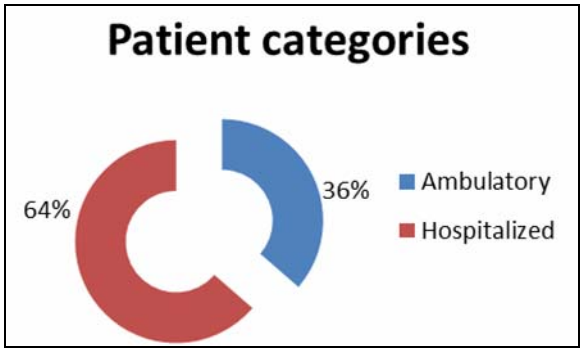


Figure 9. Patient categories.

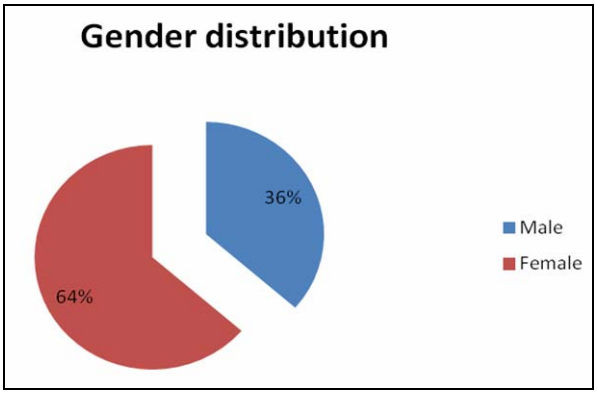


Figure 10. Gender distribution.

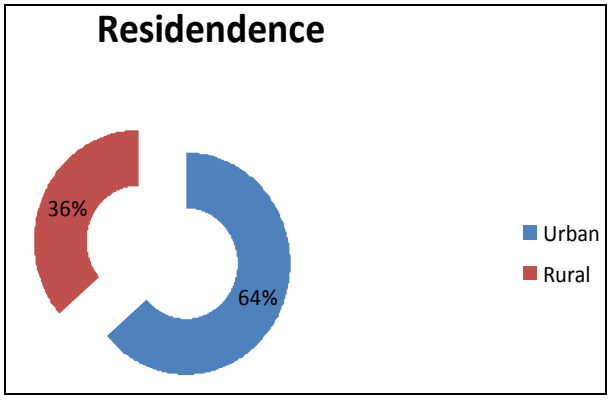


Figure 11. Residence distribution.

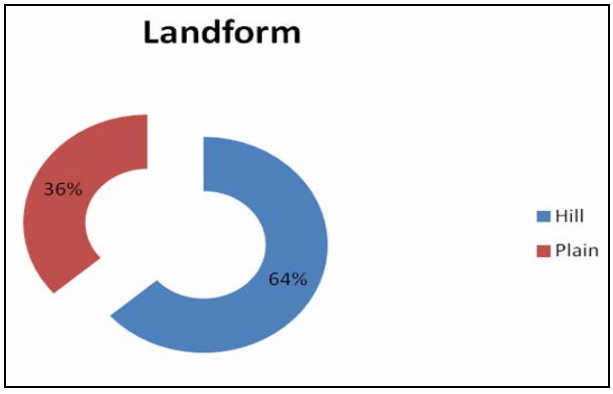


Figure 12. Landform distribution.

The serological confirmation was found in 82% of cases; 9% had negative tests and 9% had intermittent results (Fig. 13).

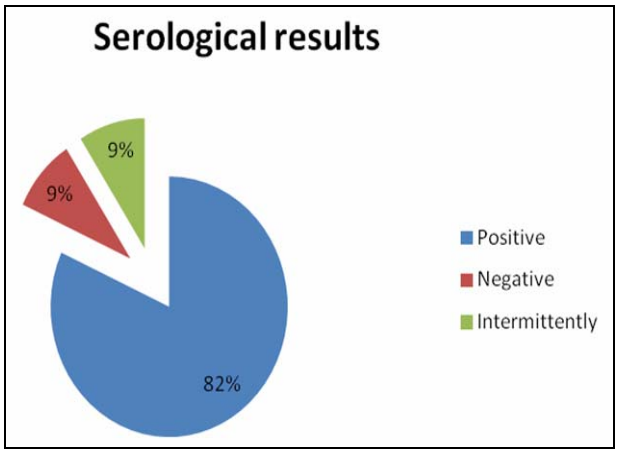


Figure 13. Serological confirmation.

55% of our patients had DFM confirmation (Fig. 14).

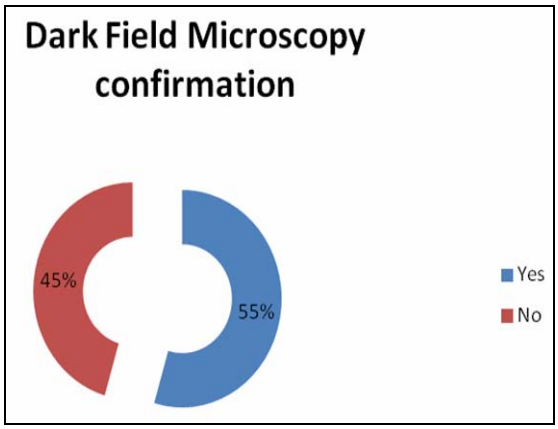


Figure 14. DFM confirmation.

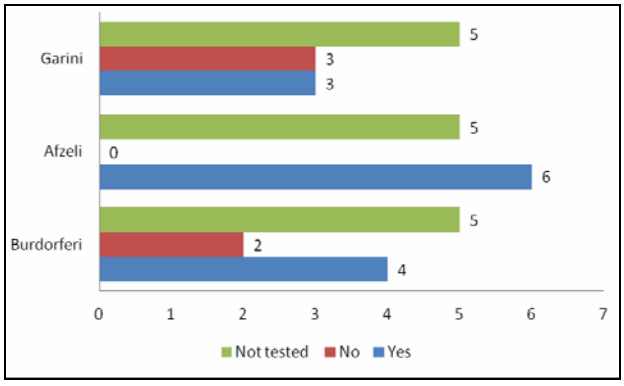


Figure 15. Strains of Borrelia distribution.

Symptomatology: sufferance types met in our study group (Fig. 19).

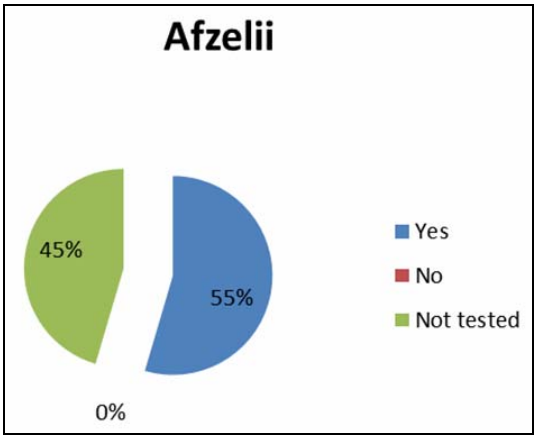


Figure 16

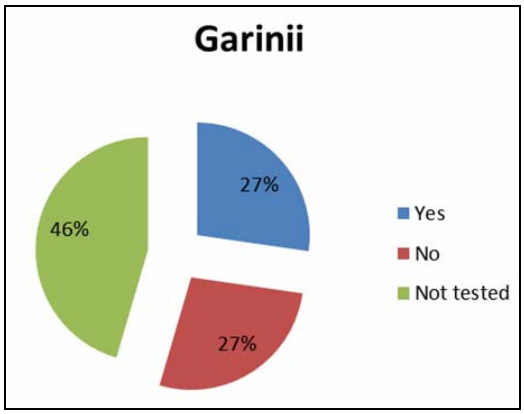


Figure 17

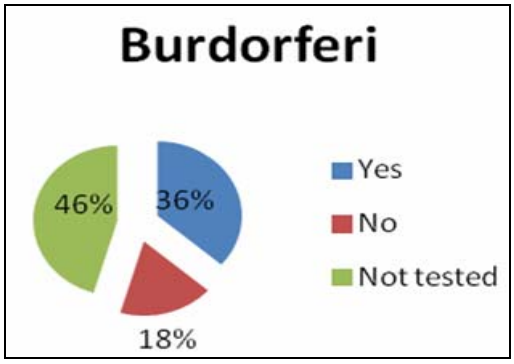


Figure 18

The Borrelia identified strains were:

- The Garinii strain was tested only in 6 cases and identified in 3 patients (27%), and not found in the other 3 tested patients (Figs. 15, 16).
- The Afzelii strain was tested only in 6 cases and identified in all of them 6 (Figs. 15, 17).
- The Burgdorferi strain was tested only in 6 cases and identified in 4 of them (Figs. 15, 18).

The most frequent symptoms were: neurologic (56%), ocular (17%), articular and psychiatric (11% each) and cardio-vascular (5%) (Fig. 20).

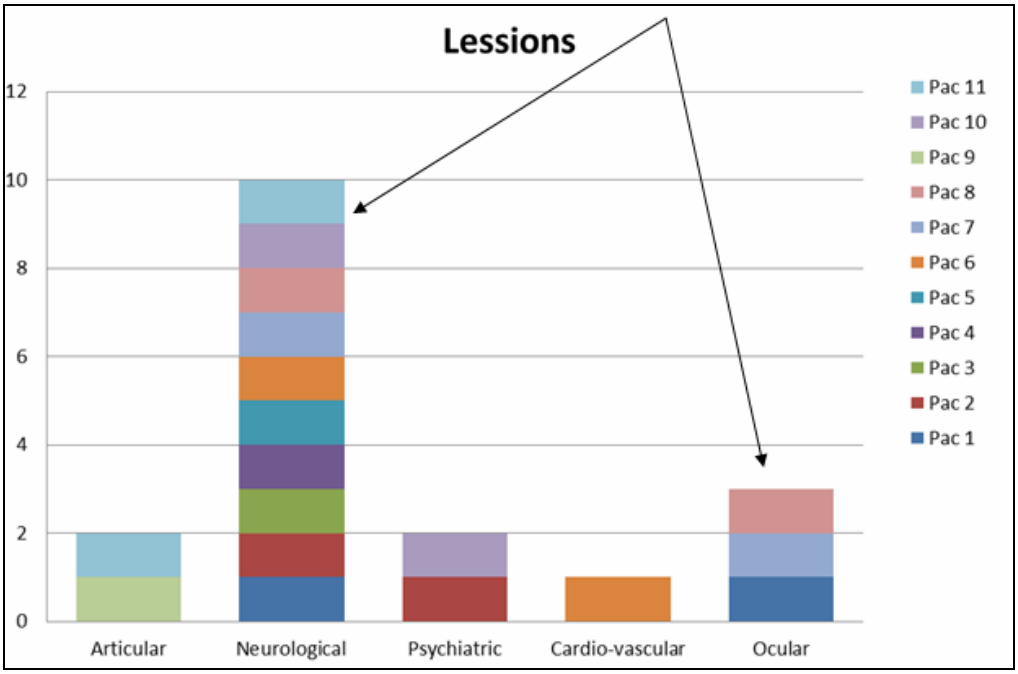


Figure 19. Symptoms of Lyme Disease from our study group.

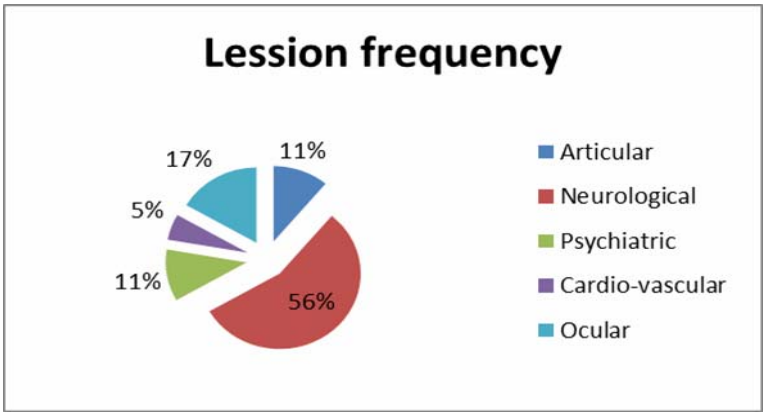


Figure 20. Symptoms frequency.

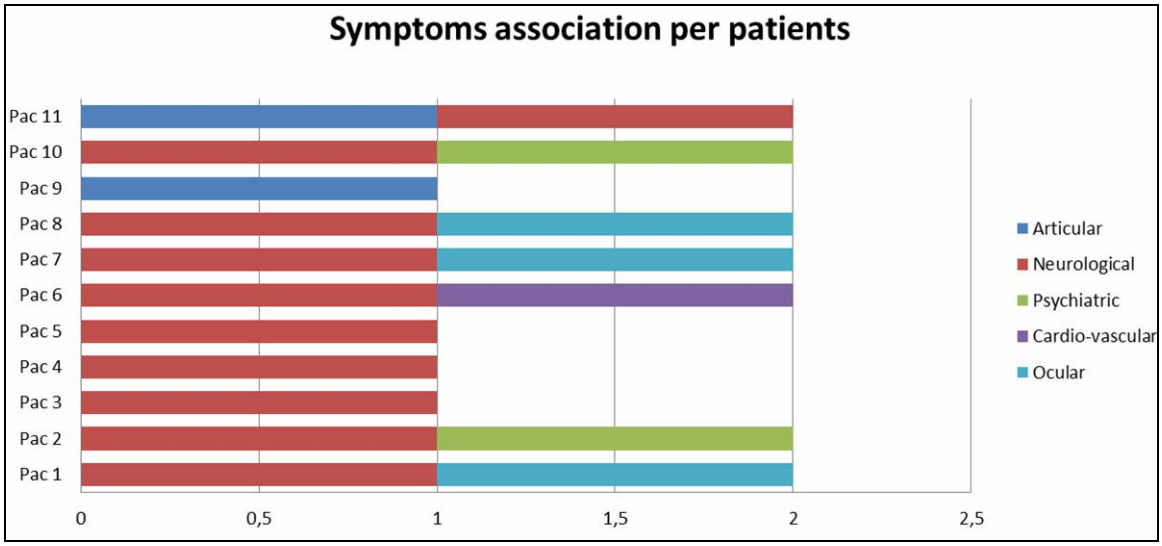


Figure 21. Symptoms association per patients.

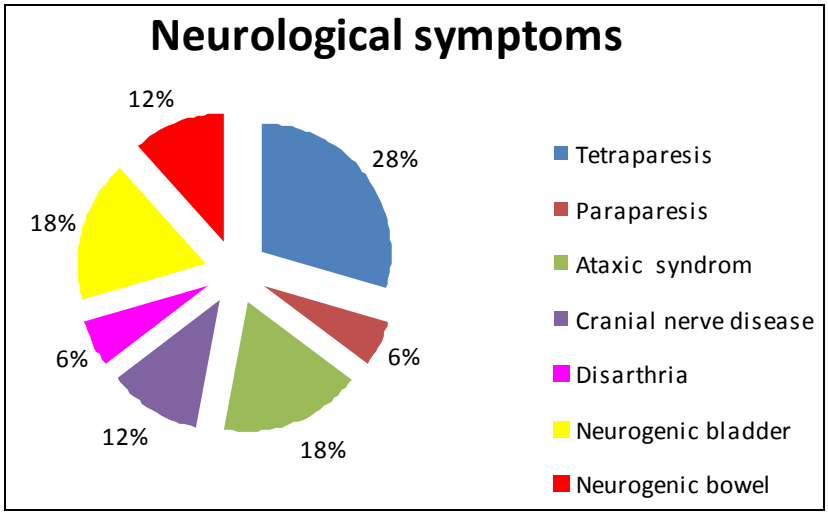


Figure 22. Neurological symptoms distribution.

The most frequent types of symptomatology associations in the studied patients were of neurologic and ocular kind (Fig. 21).

The neurologic disorder most frequently encountered by our studied patients, was the motor deficit (46 % tetraparesis and 9 % paraparesis – Fig. 22).

On cerebral MRI investigation it has been found that 18% of the studied patients had normal aspect of the examined structures and 46% showed demyelinating lesions; 36% did not perform this imaging examination (Fig. 23).

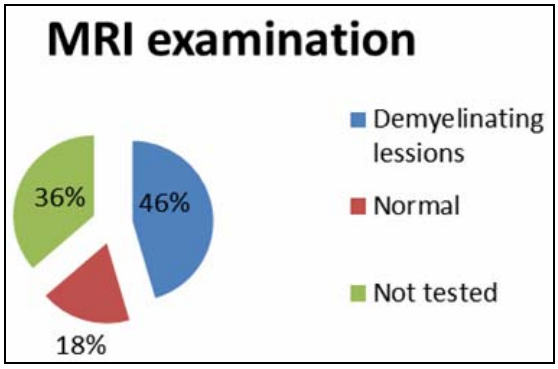


Figure 23. MRI examination distribution.

In the studied patients, the administered specific therapy was based on Ceftriaxone (to be mentioned that being a chronic, prone to recurrences, infection/ disease, the patients with borreliosis were found by us, in different stages of evolution/ time elapsed since the onset and therefore with different schemata of treatment, some of them established in other units). To be specified that the mean/average of days in between the examinations in dynamic were 92.9 days. 18% of cases received no antibiotherapy (Fig. 24).

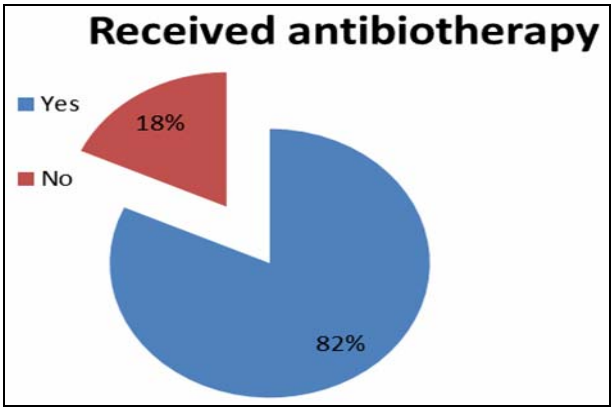
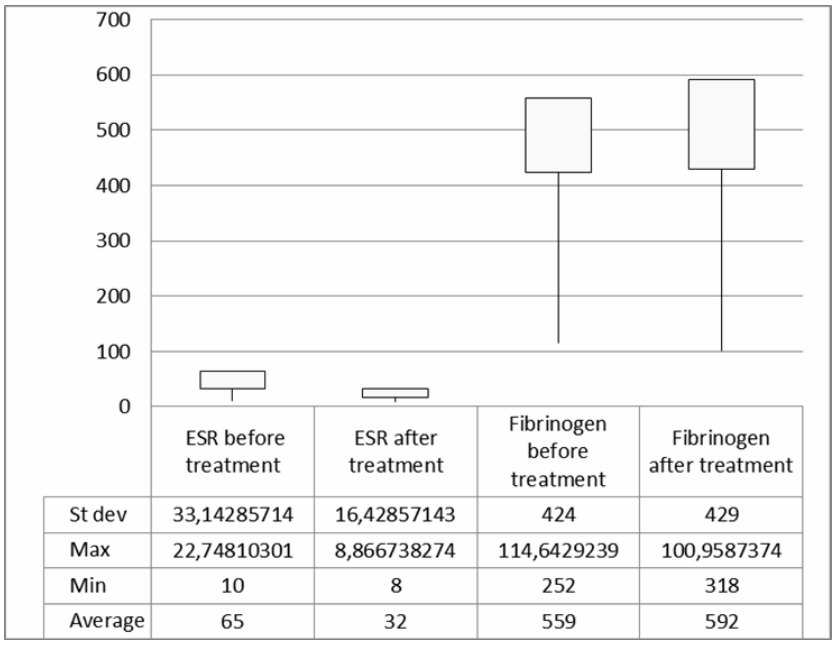


Figure 24. Received antibiotherapy.

Unfortunately, the responsiveness to therapy, meaning complete assay (clinical and biological) in both pre- and post-therapeutic conditions has been possible only in 7 of the studied patients (but implying a very complex and rigorous statistical methodology). However, considering the small number, it's increase is necessary in order to consolidate validity.

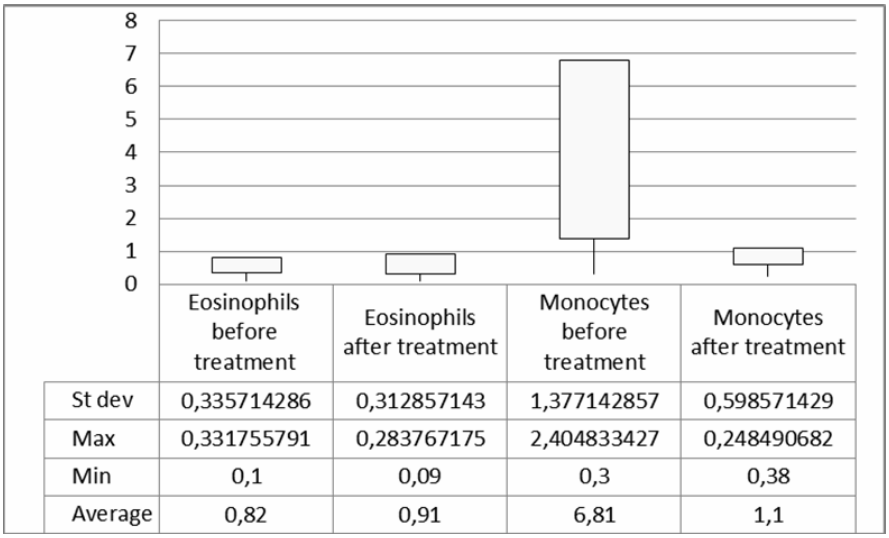
So, there have been examined from clinical and biological point of view, only the dynamically tested inpatients or outpatients before and after the antibiotherapy. Each of these 7 patients assessed pre- and post-therapy, has been his/her own witness.

The dynamics of the para-clinical examination has shown: significantly lower ESR values after treatment (Fig. 25).



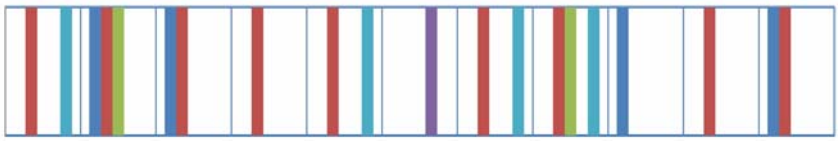
	ESR before treatment	ESR after treatment	Fibrinogen before treatment	Fibrinogen after treatment
St dev	33,14285714	16,42857143	424	429
Max	22,74810301	8,866738274	114,6429239	100,9587374
Min	10	8	252	318
Average	65	32	559	592

Figure 25. ESR and Fibrinogen values before and after treatment.



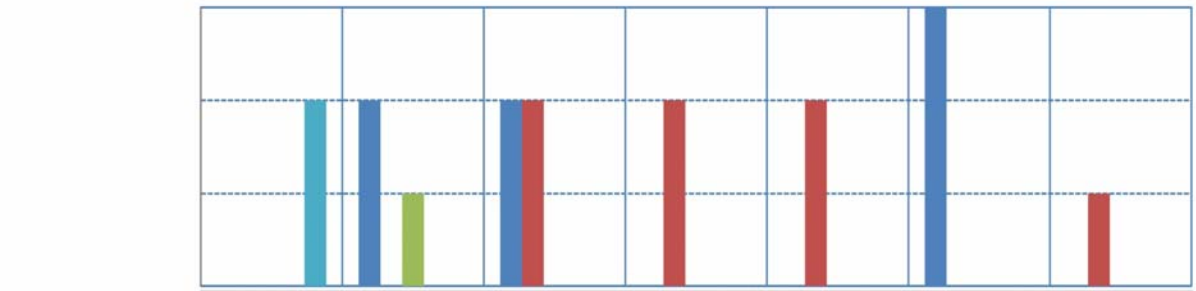
	Eosinophils before treatment	Eosinophils after treatment	Monocytes before treatment	Monocytes after treatment
St dev	0,335714286	0,312857143	1,377142857	0,598571429
Max	0,331755791	0,283767175	2,404833427	0,248490682
Min	0,1	0,09	0,3	0,38
Average	0,82	0,91	6,81	1,1

Figure 26. Eosinophils and Monocytes values before and after treatment.



	Pac 1	Pac 2	Pac 3	Pac 4	Pac 5	Pac 6	Pac 7	Pac 8	Pac 9	Pac 10	Pac 11
Articular	no	YES	YES	no	no	no	no	no	YES	no	YES
Neurological	YES	YES	YES	YES	YES	no	YES	YES	no	YES	YES
Psychiatric	no	YES	no	no	no	no	no	YES	no	no	no
Cardio-vascular	no	no	no	no	no	YES	no	no	no	no	no
Ocular	YES	no	no	no	YES	no	YES	YES	no	no	no

Figure 27. Symptoms associations per patients: YES/no.



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 9	Patient 10
Articular	no	2	2	no	no	3	no
Neurological	0	0	2	2	2	no	1
Psychiatric	no	1	no	no	no	no	no
Cardio-vascular	no	no	no	no	no	no	no
Ocular	2	no	no	no	no	no	no

Figure 28. Dynamic tested patients' evolution.

Concerning the variation "before" and "after" treatment of the eosinophils values, considering the resulting $p = 0.5$ this places such an outcome in statistical "absolute ambivalence".

Other investigated parameters showed no significant changes and respectively, fibrinogenemia, glicemia, triglycerides, leucocytes, neutrophils and MCHC, emphasized p values rather suggestive for lack of change between "before" and "after" therapy.

We have tested the clinical responsiveness to the received therapy using a customized scale on 7 degrees:

Table 1

A customized scale on 7 degrees

Value	Symptomatology
–3	severe deterioration
–2	important deterioration
–1	mild/ moderate deterioration
0	← **baseline** → stationary
1	mild/moderate improvement
2	important improvement
3	remission

According to the Wilcoxon Signed Rank test, the antibiotherapy despite ties for two patients produced statistically significant decrease of ESR values ($p = 0.042$). To be also noticed that the mean decrease of 16.7 units (std. dev. = 20.2) induce a 95%-confidence interval (–2, 35.4) for the decrease, but the data cannot be accepted as nearly normal.

DISCUSSION

As afore mentioned the statistical outcomes regarding the dynamics of the eosinophils number values showed a statistical "absolute ambivalence". In case that on an extended study on more patients, with consequent higher statistical power it will appear a significant tendency to their increase, we could discuss an interesting observation found in the literature: "possible Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome in a child with borreliosis". Specifically, such an increase might represent a stress for the body's immune tolerance by antibioteraphy in a Borrelia infected organism[4]. Additionally, from our own related, including to this study, clinical expertise we observed, in one of the antibiotic treated patients the appearance of an allergic blefaro-conjunctivitis, but after ending the treatment.

A possible limitation of the study – aside the small number of cases considering a related objective/ inevitable amount of distortion in the numerical outcomes – regards the large deviation from the mean of the number of days within the period "before"-"after" the treatment, in one case (478 days). Taking into account the basic need for

statistical power, we preferred not to exclude this case which could make the studied lot too small, thereby prone to impair statistical accuracy.

CONCLUSIONS

The disease approached in this study, although in principle, generally curable because it's bacterial etiology, remains – as herein presented – a complicate, difficult medical challenge, with considerable disabling potential; thus, including with its tendency to recurrences and respectively, epidemiological features, it makes it a public health matter.

Antibiotic therapy applied in *Borreliosis*/Lyme disease has, as positive aspects, the lowering of ESR and its significant predictivity for the improvement of neurological symptoms, and also possible – but completely doubtful – negative ones: the equivoque related afore mentioned variation of eosinophils values.

Hence, more precise and earlier diagnosis of this disease is both, a complicated but so necessary endeavor: better results can be obtained if the appropriate treatment is promptly given to the patients, but also avoiding multiple and prolonged antibiotherapy if this isn't necessary, represents itself, a medical and socio-economic goal.

As previously mentioned, is necessary to continue this study on a larger lot of patients.

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