

Diagnosis and treatment in patients with chronic Tick Associated Poly-Organic Syndrome (TAPOS) - a case series

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Abstract. Chronic Lyme borreliosis is often considered as a diagnosis option in patients with long lasting miscellaneous symptoms after tick bites. Despite new codified diagnosis algorithm and treatment, persistent signs and symptoms frequently occur. The aim of the study was to assess the diagnosis of Tick Associated Poly-Organic Syndrome (TAPOS) and to evaluate the treatment's efficacy. A consecutive case series of patients referred to the Cluj-Napoca University Hospital of Infectious Diseases (January 2006-October 2009) revealed 54 patients with TAPOS. Inclusion criteria consisted of: more than 18 years of age, chronic symptoms, positive *Borrelia burgdorferi* serology and/or tick bite. Data was collected through chart review and medical observation. We used two clinical scores to classify the probability of chronic TAPOS. All patients were tested for IgM and/or IgG antibodies to *B. burgdorferi*. The treatment was done with intravenous ceftriaxone, 2 g, daily, for 21-28 days and doxycycline 200 mg, daily, for 21 days. The most frequently reported symptoms were neuropsychological (87%), systemic (81%), muscular and/or articular (33%). The sex ratio was 0.26 (42 women, 12 men), the average age was 43.7. Only eight patients experienced erythema migrans, 20 had tick bite history (51%) and *B. burgdorferi* serology was positive for IgM (92%) and/or IgG (47%). Chronic TAPOS was diagnosed in 19 patients (35%), the remaining being with "probable" disease.

Keywords: *Borrelia burgdorferi*; Lyme borreliosis; TAPOS.

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Introduction

Lyme borreliosis is a controversial disease which is easily diagnosed and treated during the early, localized cutaneous stage. After

secondary dissemination it might evolve in a chronic and difficult to treat miscellaneous disease (Aguero-Rosenfeld, 2005; Aberer, 2007). The existence of late Lyme borreliosis is a subject of continuous debate in the last two

decades because the infection is considered rare and there is no formal test for the diagnosis. Serology, as the main diagnostic tool, should be interpreted cautiously due to certain limitations regarding sensitivity and specificity (Cairns and Godwin, 2005; Evans et al., 2005). There is a mixture of patients with chronic symptoms having a documented history of erythema migrans, but still serologically negative. However, in others, with probable chronic Lyme borreliosis and without known tick bite history, the diagnosis is considered positive due to serology (Halperin, 2005; Feder et al., 2007). The controversy leads to either restrictive recommendation for treatment according to the guidelines released by the Infectious Diseases Society of America (IDSA) or unnecessary prolonged antibiotic therapy with risks outweighing the benefits (Steere et al., 2004; Wormser et al., 2006). Beyond the controversy, there is growing scientific evidence that chronic Lyme borreliosis does exist and it is associated with persistent infection with *B. burgdorferi*. The chronic infection leads to persistent musculoskeletal, neurological and cardiac symptoms, all related to the ability of the spirochetes to escape or to suppress the immune response through different mechanisms (Brorson et al., 2001; Fritzsche, 2005; Feder et al., 2007). The most common mechanisms include: (1) genetic diversity and differential expression of the antigens that spirochetes express in mammalian hosts (i.e. OspC, other gene products - VlsE); (2) production of a protective layer (i.e. a capsule similar to the one of *Treponema pallidum*); (3) production of cystic forms (L-forms); (4) induction of incomplete or modified immune response; (5) presence of other pathogenic factors which allow immune evasion (i.e. motility, host proteases used for invasion, deleterious activity on neutrophil function, differential expression of the Toll-like receptors, breaking through barriers, etc.).

The basis for a prolonged treatment is that once the chronic infection in protected tissues is established, the longer the treatment with antibiotic the most beneficial might be. The recently published studies upon the efficacy of long-term antibiotic treatment and randomized placebo-controlled trials are in favor of the extended treatment for chronic Lyme

borreliosis (Cameron, 2008; 2009; Clarissou et al., 2009).

The diagnosis of persistent Lyme borreliosis is suggested by a history of remote tick bite and/or erythema migrans, symptoms involving various organs and a positive *B. burgdorferi* serology (Günther and Haglund, 2005; Wormser et al., 2006). The two-tier Lyme test system requires a patented commercially-available IgG immunoassay followed by a confirmatory Western Blot. The test system has a high specificity but a sensitivity of 8-56% (Feder et al., 2007; Stricker and Johnson, 2009). Even after the new recommendations for antibiotic treatment, many patients complain of persistent symptoms, the syndrome of post-treatment Lyme borreliosis being defined by fatigue, myalgia, paresthesia and mood disorders (Kuiper, 2004; Greer et al., 2007; Pachner and Steiner, 2009). The explanation is related to immune evasion or to co-infection with other tick-borne pathogens (bacteria, viruses or protozoans). The autoimmune response triggered by the eradicated *Borrelia* infection is not supported by scientific evidence (Stricker and Johnson, 2009). Since the etiology and the duration of the optimal antimicrobial therapy in one or repeated regimens is uncertain and there is no clear distinction between the persistent Lyme borreliosis and the post-treatment Lyme borreliosis, we consider appropriate the term „Tick Associated Poly-Organic Syndrome” (TAPOS) introduced by Clarissou et al. (2009).

The aim of the study was to describe a group of consecutive patients that were diagnosed and treated for chronic TAPOS, to evaluate the clinical manifestations and to assess immediate and long-term outcome.

Materials and methods

We retrospectively analyzed all patients being consecutively admitted in the University Hospital of Infectious Diseases between January 2006 and October 2009. Diagnosis was based upon clinical signs lasting for more than six months, with positive serological testing for IgM and IgG (ELISA), followed by confirmatory Western Blot. All patients were at least 18 years of age. The questionnaire included a

history of tick exposure, tick bite and erythema migrans. The immune blotting assay was interpreted as IgM positive if reactivity to OspC, VlsE and p39 antigens and as IgG positive if reactivity to VlsE, p 83 and other antigens was found. For each case, two probability scores were calculated based upon exposure, clinical and serological criteria. The first scoring system was released by Centers for Disease Control (CDC) and stratified as: (1) very probable Lyme borreliosis for 7 or more than 7 points; (2) probable with 5-6 points; and (3) not probable for 4 or less than 4 points (table 1).

Table 1. The scoring system used (after CDC)

Sign	Points
Tick exposure	1
History of disease, suggestive for borreliosis	2
Systemic involvement (no other diagnosis)	
one system, e.g. arthritis	1
two systems, e.g. arthritis and facial palsy	2
Erythema migrans confirmed by physician	7
ACA confirmed through biopsy	7
Seropositivity/Seroconversion	3/4
Silver stain microscopy/IFA	3/4
Positive culture	4
Identification of <i>B. burgdorferi</i> antigens	4
Identification <i>B. burgdorferi</i> nucleic acids	4

We alternatively used a score published in by Klempner et al. (2001) which classifies patients with very probable (more than 9 points), probable (5-9 points) and little probable (less than 5 points) chronic TAPOS. The score consisted of erythema migrans (5 points), positive *B. burgdorferi* serology (5 points), tick bite (3 points), several organ categories signs and symptoms (2 points), one organ category signs and symptoms (1 point). Patients were treated for at least 3 weeks with ceftriaxone shifted to oral therapy with doxycycline, for 6 weeks. Some of them were re-treated with the same regimen. All data was collected and analyzed in the Epi Info 2000 software.

Results

Clinical picture at admission

Fifty-four patients were included in the study with a probable diagnosis of chronic Lyme borreliosis. Tick exposure or tick bite was

identified in 28 patients (51%), a history of erythema migrans in 8 (14%), 20 patients (37%) did not reported tick exposure. The average age was 43.7 (CI 95: 39-47) and the sex ratio was 0.28 (42 women and 12 men). General signs at admission were dominated by poor stamina and/or asthenia in 44 patients (81%), and none presented recurrent fever. The majority presented neuropsychological signs and/or cognitive impairment (47-87%), paresthesia (41-76%), headaches (30-55%), paralysis (14-26%), vertigo (23-42%), ataxia or impaired walk (14%), combined neurological symptoms and cognitive impairment (i.e. memory disorders, depression, sleep disorders) (17-31%). Articular (polyarthralgia or recurrent arthralgia) and muscular signs (fasciculations and muscular weakness) were present in 18-33%. Besides general symptoms and signs, two types of organ category of signs and symptoms (neuropsychological and articular) were present in 9 patients (16%). Except tachycardia, other cardio-respiratory signs and symptoms were not found or could not be associated to spirochete infection. Thyroid disorders were found in three patients and five depression syndromes with prolonged treatment were diagnosed.

Using both scores we obtained the same probability of having chronic Lyme borreliosis, namely: 19 cases (35%) were classified as "very probable" and the other 35 as "probable". Serology was done according to the recommendations universally accepted in a two-step process: screening enzyme immunoassay that was always performed and then a Western Blot test for confirmation. All the patients had a positive serology either for IgM or IgG or both through enzyme immune assay. The concordance of IgM antibodies identified by 2-test approach was of 90% (table 1). The concordance of IgG antibodies identified by 2-test approach was of 87.8% (table 2). Among the 54 cases, 28 (51%) were confirmed through immune blotting assay, 13 patients did not have a positive confirmatory test and the remaining were not tested through Western Blot. All patients had a positive *B. burgdorferi* serology, 41 patients (76%) were found positive just with the screening test.

Table 2. IgM serology in patients diagnosed with chronic Lyme borreliosis

IgM ELISA	IgM Western Blot or Line Blot	
	Positive	Negative
IgM +	50	34
IgM -	4	1
Total	54	35

Table 3. IgG serology in patients diagnosed with chronic Lyme borreliosis

IgG ELISA	IgG Western Blot or Line Blot	
	Positive	Negative
IgG +	24	18
IgG -	27	1
Total	51	19

Neuroimaging was performed in 20 cases in which diagnostic was otherwise challenging. In 10 patients, Magnetic resonance imaging (MRI) was normal while in the rest of them (range of age 36-53 years) two or more brain white matter abnormalities were reported in T2 and FLAIR, with periventricular disposition. Cerebral edema was never present. Complete resolution of the brain lesions was observed in three patients, 3-6 months after the treatment. Two were diagnosed with probable multiple sclerosis and the other were not yet evaluated after treatment.

All patients received ceftriaxone 2 g/day for 21-28 days and 12 patients continued with doxycycline 200 mg/day for 21 days. No cases of clinical aggravation or serious adverse events were reported, except three patients that developed gallbladder problems and were shifted to cefotaxime 4 g/day, complete regimen ceftriaxone-cefotaxime for 21 days. All patients were hospitalized at least for the beginning of the treatment and mild exacerbation of signs was observed in about half of them. These were interpreted as Jarish-Herxheimer syndrome. At the end of the treatment, 40 patients had improved condition with less prominent general signs, less neurological symptoms (paresthesia, headache), less muscular weakness, no arthralgia and better mood. Fifteen patients revealed no benefits after treatment, eleven being re-treated with the same regimen, 1-3 times at short intervals of less than three

months. Among the unsuccessfully treated patients, 10 patients were classified as “probable” and 5 as “very probable”. Re-treatment with the same regimen did not improve the evolution and for some of them repeated treatments were done mostly at their request despite lack of results. All the patients that were reevaluated serologically (at request or because of unfavorable outcome) remained with a positive IgM and/or IgG response.

Discussions

Late stage Lyme borreliosis is a challenging diagnosis but it is more and more considered in case of long-lasting miscellaneous symptoms after a tick bite or if another diagnosis is not explanatory. The debate is more acute between the two options: prolonged and/or repeated treatments or no treatment since chronic Lyme borreliosis does not exist and the increasing incidence seems more “faith based” than “evidence based” (Klempner et al., 2001; Stricker and Johnson, 2009). Beyond the medical controversy, there is a public opinion that long lasting symptoms diagnosed as probable late Lyme borreliosis need more attention and appropriate medical care. Until now, the TAPOS is not well defined, the pathophysiology is not clear and the name of chronic Lyme borreliosis is not relevant. Therefore we appreciate that the denomination “chronic TAPOS” introduced by Clarissou et al. (2009) is appropriate even if the criticism might be that in many cases tick bite or erythema migrans are not described. We retrospectively studied patients that were diagnosed with TAPOS based on a case definition including long lasting signs and symptoms and a positive 2-test approach for *B. burgdorferi* serology. The descriptive analysis of our patients shows remarkable similarities with other studies performed in Europe: adults, more women than men, corresponding classically to the second peak of Lyme borreliosis but without satisfactory explanation for the female predominance, since late disease is not considered to be due to autoimmunity (Kuiper, 2004; Clarissou et al., 2009). A positive history of tick exposure and/or erythema migrans was found only in 51% of all patients corresponding to published data (Clarissou et al., 2009). The explanation is

well known: unperceived tick bite or recall bias. The history of erythema migrans is certain; therefore it is included in all scoring systems. Using both scores we classified our patients as being “very probably” or “probably” diagnosed with TAPOS. None had a “less probable” diagnosis. The degree of confidence that symptoms were related to tick exposure (even unnoticed some times) was quite high. It is also well known that the testing for Lyme borreliosis is “questionable” and the sensitivity for enzyme immune assay is ranging from 8 to 56%. The 2-test approach confirmed the diagnosis in half of the patients but taking into consideration the degree of concordance between the tests, most patients can be assumed as having a positive serology.

We have to mention that inclusion of the 41 and 58kDA bands as specific ones was introduced in the laboratory only in 2008. Line blot assays have a higher sensitivity especially for IgM antibodies: 73.8% compared to 40% Western Blot. Not all, but many patients were tested for Epstein-Barr virus infection and auto-antibodies and none except one was positive for autoimmune thyroid disorder. Better testing does not seem applicable in the near future. The clinical signs and symptoms at admission were partially similar to other European studies: predominance of neurological, psychiatric and general signs and, on the contrary, we found just a few cases having digestive and cardio-respiratory signs (Kuiper, 2004; Clarissou et al., 2009). We observed that the hallmark in our cases of chronic TAPOS was a combination of poor stamina/fatigue, paresthesia and persistent headache. We found less articular complains corresponding to the higher affinity for nervous tissue of spirochete genospecies circulating in Europe (*B. garinii* and *B. afzelii*).

Occult modifications in white and grey matter are present in patients with TAPOS demonstrating the tissue damage: small hypointense lesions in T1, hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) being hyper- or hypometabolic in functional MRI (fluorodeoxyglucose) (Steinbach et al., 2005; Agosta et al., 2006). The abnormal lesions are located in the cortex, subcortex, deep white matter, subcortically,

mainly in the frontal and temporal lobes and in the basal nuclei. In recent studies upon patients with late Lyme borreliosis presenting focal symptoms neuroimaging demonstrated the presence of multiple sclerosis-like lesions. In stark contrast to what is found in multiple sclerosis, the measures for tissue integrity were normal in patients with neuroborreliosis (Batinac et al., 2007; Sormani et al., 2008). Structural and functional MRI evaluation demonstrates the delayed resolution of white matter changes following the treatment of TAPOS (Agosta et al., 2006; Batinac et al., 2007). Delayed resolution of cerebral tissue is sometimes observed and only repeated structural and functional neuroimaging can demonstrate the benefits of the etiologic treatment. We used a treatment recommended by Wormser et al. (2006) with ceftriaxone shifted to doxycycline, a 6 week-regimen. It was very difficult to ascertain the treatment benefits since many problems were subjective but we appreciate treatment as being beneficial. Still, 20% of our patients were coming again for treatment due to many reasons besides persistence of some symptoms: “Lyme hysteria” and persistent positive serology. As other authors observed in long-term follow up studies, positive serology might last for decades, therefore does not represent a criteria for treatment benefits (Kalish et al., 2001). We cannot appreciate the optimal duration of the treatment but since no patient experienced a severe adverse event we conclude that a 6-week regimen is reasonable and it is close to the nowadays attitude of reducing the longer treatments considered before.

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