

LYME BORRELIOSIS AND MULTIPLE SCLEROSIS: ANY CONNECTION? A SEROEPIDEMIC STUDY

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Abstract: A total of 769 adult neurological patients hospitalised in clinics and hospitals situated in the Lublin region (eastern Poland) were examined during the years 1997–2000 with ELISA test for the presence of anti-*Borrelia burgdorferi* sensu lato antibodies. A statistically significant ($p = 0.0422$) relationship was found between the clinically confirmed diagnosis of multiple sclerosis and the positive serologic reaction with *Borrelia* antigen. Ten out of 26 patients with multiple sclerosis (38.5%) showed positive serologic reaction to *Borrelia*, whereas among the total number of examined neurological patients the frequency of positive findings was twice as low (19.4%). The result suggests that multiple sclerosis may be often associated with *Borrelia* infection.

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INTRODUCTION

Lyme borreliosis (LB) is a multisystemic tick-borne illness caused by neurotropic spirochete *Borrelia burgdorferi* sensu lato. Two of the 3 stages of LB may involve the central nervous system (CNS): a second stage that may manifest as meningitis, cranial neuritis or radiculoneuritis; and a third (tertiary) stage, or chronic neuroborreliosis with parenchymal involvement [13]. The tertiary stage of LB may mimic multiple sclerosis (MS) and some other CNS conditions, including polyneuropathy, viral encephalitis, brain tumour, vasculitis, encephalopathy, and psychiatric illness [9, 13, 14].

Both in LB and MS predominantly white matter is affected and the clinical differentiation between these entities, even with the use of magnetic resonance imaging (MRI), is very difficult [22]. There is no specific laboratory test in MS [5, 20] and the diagnosis is based largely on symptomatology whilst in LB the presence of specific antibodies is of key diagnostic value. Because of the growing sociomedical importance of both diseases,

the determining of their mutual relationship is a subject of a particular scientific interest [4, 5, 6, 8, 9, 11, 14, 16, 20, 21, 22, 24]. This is also true in Poland where the annual number of LB cases has grown from 751 in 1996 [2] to 891 in 1999 [12]. The serologically proved infections with *Borrelia burgdorferi* are most common among foresters, agricultural workers and other persons occupationally exposed to attack of *Ixodes ricinus*, the LB vector in Europe [1]. On the other hand, the number of MS sufferers in Poland is about 60,000 persons [17] which creates a severe sociomedical problem.

The aim of the present work was to analyse the relationship between the clinically confirmed diagnosis of multiple sclerosis and occurrence of positive serologic reaction to *Borrelia burgdorferi*, the causative agent of Lyme disease.

MATERIALS AND METHODS

Patients. A total of 769 adult neurological patients with various diagnoses were examined for the presence of

anti-*Borrelia burgdorferi* sensu lato antibodies during the years 1997-2000. The patients were hospitalised in 12 clinical units: in two clinics in the city of Lublin and in 10 hospitals situated in the Lublin region (eastern Poland). Twenty six patients, were diagnosed with multiple sclerosis, based mainly on the characteristic symptomatology (including paralysis of lower limbs) and the results of magnetic resonance imaging. Twenty five patients were diagnosed with Lyme neuroborreliosis based on the result of serological examination, tick bite history and symptomatology.

Serological examination. Sera of the patients were examined by the immunoenzymatic assay (ELISA) using a commercial set "Enzygnost Borreliosis" for IgM and IgG antibodies (Behring, Marburg, Germany). In this assay, detergent extract from a mix of membrane proteins from Pko strain *Borrelia afzelii*, isolated in Europe from skin, was used as an antigen. The mixture of antigens includes at least the proteins: 100 kD, 41 kD, 39 kD, Osp A, Osp B, Osp C and 17 kD. This ensures very high sensitivity of the assay in all stages of the disease. Specificity was increased by the addition of *Treponema phagediens* ultrasonificate in sample buffer which decreases frequency of cross reactions. Assay was read in ELISA reader with a 450 nm filter. A result was considered as positive if absorbance was greater than cut-off evaluated according to the instruction [1]. In the Behring scale, the considering of the result as positive was recommended from 9 units/ml.

Statistical analysis. The results were analysed with the Yates corrected chi-square test, using the statistical package STATISTICA for Windows v. 4.5 (©Statsoft, Inc., USA). The value of $p < 0.05$ was considered as significant.

RESULTS

A statistically significant ($p = 0.0422$) relationship was found between the clinically confirmed diagnosis of multiple sclerosis and the presence of anti-*Borrelia* antibodies in ELISA test (Tab. 1). Ten out 26 patients with multiple sclerosis (38.5%) showed positive serologic reaction to *Borrelia*, whereas among the total examined neurological patients the frequency of positive findings was twice as low (19.4%).

An example of the positive anti-*Borrelia* reaction in the patient with clinically confirmed multiple sclerosis is presented in Table 2. The patient had been observed from October 1995–November 1998 and therefore the tests made in the period preceding the main study (1995–1996) were carried out with the simpler, semiquantitative ELISA assay (Biomedica, Vienna, Austria). The presence of IgG antibodies to *Borrelia* was found, indicating the past infection, probably in summer 1995. The level of the IgG anti-*Borrelia* antibodies increased during 1996 and remained high also during following years (1997-1998).

Table 1. Clinical diagnosis of multiple sclerosis versus seropositive ELISA reaction to *Borrelia burgdorferi* in neurological patients: frequency of observed cases in 2×2 chi-square table.

	Multiple sclerosis diagnosed +	Multiple sclerosis not diagnosed (-)	Total
Reaction to <i>B. burgdorferi</i> positive +	N = 10	N = 149	N = 159
Reaction to <i>B. burgdorferi</i> negative (-)	N = 16	N = 594	N = 610
Total	N = 26	N = 743	N = 769
Result of chi-square test	Yates corrected chi-square = 4.13		p = 0.0422

Table 2. Results of serological examination with *Borrelia burgdorferi* in a patient with the diagnosis of multiple sclerosis.

Patient M.K., female, born 1949			
Test	Date of examination	IgM	IgG
ELISA Biomedica ^a	20-10-1995	(-)	(-)
	29-03-1996	(-)	+
	05-07-1996	(-)	++
	22-11-1996	(-)	+++
ELISA Behring ^b	29-01-1997	(-)	31 units/ml
	03-11-1998	(-)	27 units/ml

^asemiquantitative test for IgM and IgG antibodies, intensity of the reaction denoted + - ++++; ^bqualitative test for IgM antibodies, quantitative test for IgG antibodies.

This case illustrates well the possibility of the development of concomitant *Borrelia burgdorferi* infection in the MS patient.

DISCUSSION

The possible relationship between multiple sclerosis and Lyme borreliosis is a matter of controversy since the years following the identification of LB agent, *Borrelia burgdorferi* sensu lato. As early as in 1986, Kurtz [10] expressed a view that this spirochete may be one of the major causes of MS. The opposite view is presented by Schmutzhard [18] and Coyle [3] who negated any association between LB and MS. However, the latter view has been challenged by Lana-Peixoto [11] and Garcia-Monco *et al.* [5] who found serological evidence of the infection with LB agent in MS patients. Stelmasiak *et al.* [21] found the presence of anti-*Borrelia* antibodies in 87 out of 161 patients with suspected MS (54.0%).

In this study, a statistically significant relationship was found between the clinical diagnosis of MS and the presence of antibodies against LB agent, which supports

the view on the possible relationship between these two clinical entities. The proportion of the MS patients showing positive serological reaction to *B. burgdorferi* (38.5%) was much higher compared to the earlier studies by Coyle [3], Coyle *et al.* [4] and Schmutzhard *et al.* [19] who found respectively 1.1%, 6.7% and 14.2% positive reactions among MS patients. The difference may be partly explained by the overall high positive rate of serologic response to LB agent in eastern Poland, due to frequent exposure to bite of tick vector, *Ixodes ricinus*.

The nature of the stated relationship between infection with LB agent and MS disease remains obscure. In some cases, neuroborreliosis may be misdiagnosed as MS. A direct provoking of MS by *B. burgdorferi* does not look probable, but it cannot be excluded that the LB agent may aggravate the pathogenic processes in the initial stage of MS and thus increase a number of the symptomatic, clinically diagnosed cases. This hypothesis, similar to that proposed by Karussis *et al.* [8], may be supported by the resemblance of the pathologic processes in both diseases: activation of the lymphocytic system [6], inducing of the matrix metalloproteinases (MMPs) production [15], inducing of the autoantibodies production, including antibodies to neuronal proteins [7] and to myelin basic protein [8, 23]. In the late period of neuroborreliosis, demyelinating involvement of CNS can develop, similarly as in MS [5].

Considering certain limitations of the present work (lack of detailed clinical analyses, relatively low number of definite MS cases under study), it cannot therefore be a basis for suggestions on the nature of the stated significant relationship between LB and MS. Nevertheless, it does indicate a need for further studies on this subject.

In conclusion, the result of this study suggests that multiple sclerosis may be often associated with *Borrelia* infection.

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REFERENCES

- Chmielewska-Badora J: Seroepidemiologic study on Lyme borreliosis in the Lublin region. *Ann Agric Environ Med* 1998, **5**, 183-186.
- Choroby Zakaźne i Zatrucia w Polsce, Rok 1996 (Infectious Diseases and Intoxications in Poland, Year 1996)*. Państwowy Zakład Higieny, Warsaw 1997 (in Polish).
- Coyle PK: *Borrelia burgdorferi* antibodies in multiple sclerosis patients. *Neurology* 1989, **39**, 760-761.
- Coyle PK, Krupp LB, Doscher C: Significance of reactive Lyme serology in multiple sclerosis. *Ann Neurol* 1993, **34**, 745-747.
- Garcia-Monco JC, Miro Jornet J, Fernandez Villar B, Benach JL, Guerrero Espejo A, Berciano JA: Multiple sclerosis or Lyme disease? a diagnosis problem of exclusion. *Med Clin (Barc)* 1990, **94**, 685-688 (In Spanish).
- Heller J, Holzer G, Schimrigk K: Immunological differentiation between neuroborreliosis and multiple sclerosis. *J Neurol* 1990, **237**, 465-470.
- Kaiser R: Intrathecal immune response in patients with neuroborreliosis: specificity of antibodies for neuronal proteins. *J Neurol* 1995, **242**, 319-325.
- Karussis D, Weiner HL, Abramsky O: Multiple sclerosis vs Lyme disease: a case presentation to a discussant and a review of the literature. *Mult Scler* 1999, **5**, 395-402.
- Kölmel HW: Differential diagnosis in human neuroborreliosis. *Zentbl Bakteriol* 1999, **289**, 687.
- Kurtz SK: Relapsing fever/Lyme disease. Multiple sclerosis. *Med Hypotheses* 1986, **21**, 335-343.
- Lana-Peixoto MA: Multiple sclerosis and positive Lyme serology. *Arq Neuropsiquiatr* 1994, **52**, 566-571.
- Meldunek Roczny 1999 o Zachorowaniach na Choroby Zakaźne i Zatruciach Związkami Chemicznymi Zgłoszonych w roku 1999 (Yearly Report on Incidence of Infectious Disease and Intoxications with Chemicals Reported in 1999)*. Państwowy Zakład Higieny, Warsaw 2000 (in Polish).
- Murray R, Morawetz R, Kepes J, el Gammal T, LeDoux M: Lyme neuroborreliosis manifesting as an intracranial mass lesion. *Neurosurgery* 1992, **30**, 769-773.
- Pachner AR: Neurologic manifestations of Lyme disease, the new "great imitator". *Rev Infect Dis* 1989, **11(Suppl 6)**, S1482-S1486.
- Perides G, Tanner-Brown LM, Eskildsen MA, Klempner MS: *Borrelia burgdorferi* induces matrix metalloproteinases by neural cultures. *J Neurosci Res* 1999, **58**, 779-790.
- Piccolo I, Thiella G, Sterzi R, Colombo N, Defanti CA: Chorea as a symptom of neuroborreliosis: a case study. *Ital J Neurol Sci* 1998, **19**, 235-239.
- Polskie Towarzystwo Stwardnienia Rozsianego (Polish Association for Multiple Sclerosis): *Report*. Warsaw 1999 (in Polish).
- Schmutzhard E: Lyme borreliosis and multiple sclerosis. *Biomed Pharmacother* 1989, **43**, 415-419.
- Schmutzhard E, Pohl P, Stanek G: *Borrelia burgdorferi* antibodies in patients with relapsing/remitting form and chronic progressive form of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1988, **51**, 1215-1218.
- Scott TF: Diseases that mimic multiple sclerosis. *Postgrad Med* 1991, **89**, 187-191.
- Stelmasiak Z, Bekiesinska-Fugatowska M, Walecki J, Janowska D, Cisak E: MRI in patients with positive boreliosis tests treated due to MS. European Society of Neuroradiology, XXII Congress and 6th Advanced Course, 17-21 September 1996, Milan, Italy. *Neuroradiology* 1996, **38(Suppl 2)**, S91.
- Triulzi F, Scotti G: Differential diagnosis of multiple sclerosis: contribution of magnetic resonance techniques. *J Neurol Neurosurg Psychiatry* 1998, **64(Suppl 1)**, S6-S14.
- Weder B, Wiedersheim P, Matter L, Steck A, Otto F: Chronic progressive neurological involvement in *Borrelia burgdorferi* infection. *J Neurol* 1987, **234**, 40-43.
- Wilske B, Bader L, Pfister HW, Preac-Mursic V: Diagnosis of Lyme neuroborreliosis. Detection of intrathecal antibody formation. *Fortschr Med* 1991, **109**, 441-446 (in German).