Journal of Alzheimer's Disease 41 (2014) 1087–1093
DOI 10.3233/JAD-130446
IOS Press

Lyme Neuroborreliosis and Dementia

Frederic Blanc[a,b,c,*], Nathalie Philippi[a,b,c], Benjamin Cretin[a,b,c], Catherine Kleitz[a,c], Laetitia Berly[a,c], Barbara Jung[a,b,c], Stephane Kremer[b,d], Izzie Jacques Namer[b,e], François Sellal[c,f], Benoit Jaulhac[g] and Jerome de Seze[a,h]

[a]*University Hospital of Strasbourg, Neuropsychology Unit, Neurology Service, Strasbourg, France*
[b]*University of Strasbourg and CNRS, ICube Laboratory and FMTS (Fédération de Médecine Translationnelle de Strasbourg) Strasbourg, France*
[c]*University Hospital of Strasbourg, CMRR (Memory Resource and Research Center), Strasbourg, France*
[d]*University Hospital of Strasbourg, Neuroradiology Service, Strasbourg, France*
[e]*University Hospital of Strasbourg, Nuclear Medicine Service, Strasbourg, France*
[f]*General Hospital of Colmar, Neurology Service, Colmar, France*
[g]*University Hospital of Strasbourg, Laboratory of Bacteriology and National Center for Borrelia, Strasbourg, France*
[h]*INSERM U119, Strasbourg, France*

Accepted 7 March 2014

Abstract.
Introduction: Descriptions of Lyme disease and dementia are rare.
Objective: To describe patients with dementia and a positive "intrathecal anti-Borrelia antibody index" (AI), specific for neuroborreliosis.
Methods: Among 1,594 patients seen for dementia, we prospectively identified and studied 20 patients (1.25%) with dementia and a positive AI. Patients underwent a battery of neuropsychological tests brain, MRI, FDG-PET, and cerebrospinal fluid (CSF) analysis. An etiological diagnosis of the dementia was made at the end of the follow-up of 5.0 ± 2.9 years.
Results: We found two groups of patients with dementia, the first ($n = 7$, 0.44%) with certain neuroborreliosis and stability or mild improvement of dementia after treatment by antibiotics and the second ($n = 13$, 0.81%) with progressive worsening of dementia, despite the antibiotics. In the second group, the final diagnoses were Alzheimer's disease (AD) ($n = 4$), AD and Lewy body disease (LBD) ($n = 3$), LBD ($n = 1$), FTLD ($n = 3$), hippocampal sclerosis ($n = 1$), and vascular dementia ($n = 1$). We did not observe any differences in cognitive test between the two patient groups at baseline. Brain MRI showed more focal atrophy and FDG-PET showed more frontal hypometabolism in the second group. Tau, p-tau, and $A\beta_{42}$ concentrations in the CSF were normal in the neuroborreliosis group, and coherent with diagnosis in the second.
Conclusion: Pure Lyme dementia exists and has a good outcome after antibiotics. It is advisable to do Lyme serology in demented patients, and if serology is positive, to do CSF analysis with AI. Neurodegenerative dementia associated with positive AI also exists, which may have been revealed by the involvement of Borrelia in the CNS.

Keywords: Alzheimer's disease, dementia, frontotemporal lobe dementia, hippocampal sclerosis, intrathecal anti-*Borrelia* antibody index, Lewy body dementia, Lewy body disease, Lyme disease, Lyme neuroborreliosis, vascular dementia

Cognitive impairment after bacterial meningitis is well known, particularly with *Treponema pallidum*, pneumococcal, and meningococcal meningitis [1]. A diffuse pattern of cognitive impairment is generally found. The cognitive sequelae of Lyme disease have been named Lyme encephalopathy [2]. This post-Lyme disease has been described in the United States but rarely in Europe, and is still debated. Lyme encephalopathy presents with subtle neuropsychological symptoms, particularly memory impairment, and

*Correspondence to: Dr. Frederic Blanc, Neuropsychology Unit and CMRR (Centre Mémoire de Ressources et de Recherche), Neurology Service, University Hospital of Strasbourg, 1, Avenue Molière, 67091 Strasbourg Cedex, France. Tel.: +33 388128638; Fax: +33 388128636; E-mails: f.blanc@unistra.fr, frederic.blanc@chru-strasbourg.fr.

ISSN 1387-2877/14/$27.50

is associated with single photon emission computed tomography hypoperfusion [3]. Brain magnetic resonance imaging (MRI) is normal in most cases but subtle lesions such as T2-weighted lesions without gadolinium enhancement in deep white matter are found in a third of patients [2]. Late Lyme neuroborreliosis comprises cerebrovascular infarcts and meningoencephalitis characterized either by a strong lymphoplasmocytic infiltrates (infiltrative form) or by the atrophic form without lymphoplasmocytic infiltrates but with progressive cortical atrophy and pure dementia, as it is also the case in general paresis [1]. Even if these descriptions are classical, the numbers of clinical cases described are really rare in the literature. These tertiary manifestations appear six months to decades following the primary infection.

Here, we describe patients with dementia for more than 6 months and a positive "intrathecal anti-*Borrelia* antibody index" (AI), in terms of cognitive tests, cerebrospinal fluid (CSF), brain MRI, brain ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and outcome following antibiotic treatment.

PATIENTS AND METHODS

We prospectively included patients with dementia and a positive AI seen at the Department of Neurology of the University Hospital of Strasbourg between September 2005 and September 2011. These patients were followed until June 2013. We used the positive AI because we and others previously demonstrated its very good specificity to diagnose neuroborreliosis [4]. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). *Borrelia burgdorferi* ELISA, AI, and western blotting were performed on serum and CSF for IgG as previously described [4].

Among 8,437 different patients seen at the Neuropsychology Unit for cognitive complaint (of patients and/or caregivers) during this period, 1,594 had a dementia (according to DSM-IV, that means patients with cognitive impairment and impaired activities of daily living). Patients with mild cognitive impairment (MCI) and subjective cognitive impairment (SCI) ($n = 6{,}843$) were excluded from this study. All demented patients have had Lyme serology. Among the 1,594 demented patients, we diagnosed 1,041 patients with Alzheimer's disease (AD) dementia. Among the 1,594 patients with dementia, we found 38 patients with positive Lyme serology in serum (see flow chart). Among them, 34 patients have had a CSF analysis and 20 patients had a positive AI. Thus we found 20 patients with positive AI among 1594 demented patients. We compared the 20 patients included with 10 healthy controls (without any cognitive complaints, with negative Lyme serology; recruited by non-specialized press).

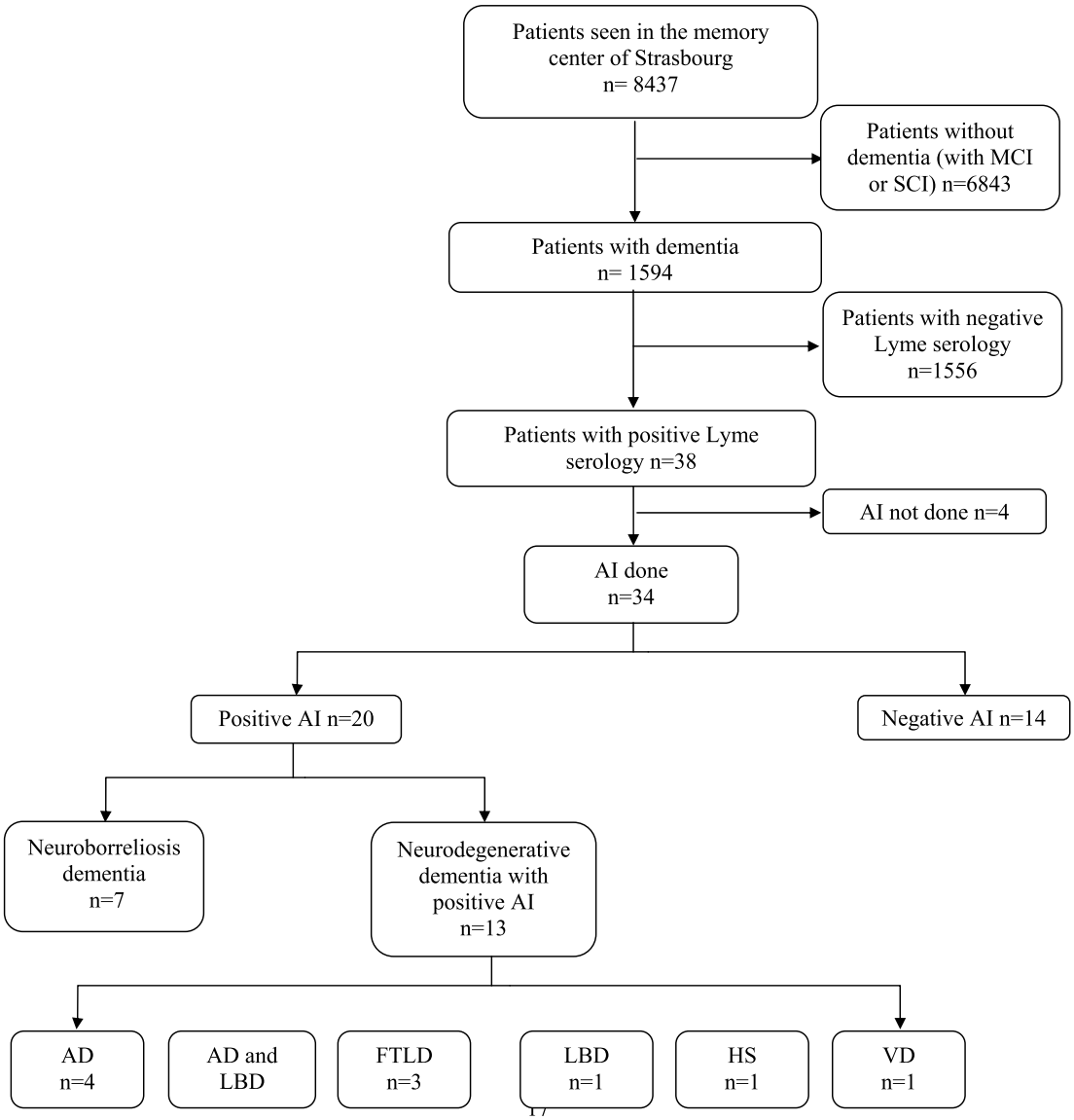
A battery of neuropsychological tests was administered to patients and controls: it included measures of global cognitive status (Mattis Dementia Rating Scale and Mini-Mental State Examination [MMSE]), executive function (Frontal assessment Battery), verbal episodic memory (Free and Cued Selective Reminding Test), the Rey-Osterrieth Complex Figure Test, and a verbal task (oral naming of 30 objects).

All patients underwent brain MRI (T1-, T2-, and T2-FLAIR-weighted sequences) and all but three underwent brain FDG-PET. CSF was analyzed in all patients. CSF analysis performed after September 2007 (i.e., 11 patients) also included measurement of tau, phospho-tau (p-tau), and amyloid-β ($A\beta)_{1\text{-}42}$ (Innogenetics's Innotest®, ELISA). White matter lesions were scored from axial FLAIR images using the semi-quantitative method of Scheltens et al. [5]. Vascular lesions were considered when the score was 5 or 6 out of 6 (i.e., a lesion greater than 11 mm or confluent lesions). An etiologic diagnosis of the dementia for each patient was made at the end of the follow-up of 5.0 ± 2.9 years (mean $\pm$ SD), using Dubois' criteria for AD [6], McKeith's criteria for Lewy body disease (LBD) [7], and Rascovsky's criteria for frontotemporal dementia [8]. Diagnosis of hippocampal sclerosis was made using clinical arguments and Barkhof's MRI scale of the hippocampus with a score of 4/4 [9].

Statistical analysis was carried out using the Kruskal-Wallis non-parametric test and Mann-Whitney U non-parametric test to compare the numerical values for each cognitive test and paraclinical results between the groups.

RESULTS

All patients received ceftriaxone 2 g/day during 3 weeks after CSF results showing a positive AI. At the end of the follow-up, 7 patients with dementia and a positive AI were stable or improved in terms of their cognitive functions and disabilities (group 1); and 13 patients with dementia and positive AI worsened (group 2). In the group 2, all patients were diagnosed with neurodegenerative disease.



Flow Chart of the present study on Lyme neuroborreliosis and dementia. Diagnosis of neurodegenerative diseases was done using diagnosis criteria of each pathology (see method). AD, Alzheimer's disease; AI, Anti-*Borrelia* Antibody Index; FTLD, frontotemporal lobe dementia; HS, hippocampal sclerosis; LBD, Lewy body dementia; MCI, mild cognitive impairment; SCI, subjective cognitive impairment; VD, vascular dementia.

Among the group 1 (i.e., "neuroborreliosis and dementia"), one patient had a stroke of the left thalamus with pure cognitive symptoms (with isolated high tau in the CSF), one other patient had a parietal hematoma of 2 cm with pure cognitive symptoms (he died three year later in a context of coronary bypass), one patient had hydrocephalus due to *Borrelia* and was also treated with shunt surgery (with normal CSF for AD markers; he died seven years later because of a cancer), four patients had predominant memory impairment with storage deficit (with normal tau, p-tau, and $A\beta_{42}$ in CSF(done for two of them), and abnormal brain PET, but not brain MRI- in the temporal lobe). Among these four patients, two began neuroborreliosis with simultaneous cognitive impairment and neural pain of lower limbs. For one of these two patients, neuropathy was objectified on electromyogram.

In group 2, thirteen patients worsened: three patients died and five other patients had an MMSE <5, four of whom were admitted to a nursing home. The final

Table 1
Clinical characteristics of patients with dementia and a positive anti-*Borrelia* AI compared to controls. Group 1 includes patients with dementia and a positive AI, without worsening after ceftriaxone. Group 2 includes patients with neurodegenerative dementia and positive AI, with worsening after ceftriaxone. The only difference between the two groups is the cognitive outcome

	Neuroborreliosis and dementia ($n=7$)/Group 1	Neurodegenerative dementia and positive AI ($n=13$)/Group 2	Controls ($n=10$)	p-value		
				Group 1 versus Group 2	Group 1 versus controls	Group 2 versus controls
Age (mean, min-max)	66.7 (43–79) ± 13.3	72.2 (53–84) ± 10.0	74.4 (65–83) ± 5.85	0.361	0.327	0.975
Gender ratio (F/M)	1/6	2/11		0.949	0.793	0.710
Educational level	10.0 ± 4.5	10.0 ± 4.9	11.6 ± 3.9	0.968	0.417	0.284
Outcome (years)	5.0 ± 2.9	5.0 ± 2.9	NA	0.872	NA	NA
MMSE/30‡	21.7 ± 6.4	17.9 ± 8.8	27.4 ± 1.35	0.283	0.006	0.001
MMSE after outcome/30§	22.1 ± 6.8	7.2 ± 11.0	NA	0.017	NA	NA
MDRS/144‡	108.3 ± 28.9	85.1 ± 52.9	141.3 ± 2.06	0.574	0.001	<0.001
attention/37§	34.2 ± 3.3	26.2 ± 15.3	36.3 ± 0.48	0.293	0.166	0.04
initiation/37‡	24 ± 11.0	19.2 ± 12.9	36.6 ± 0.97	0.425	0.004	<0.001
construction/6	5 ± 2.4	4.4 ± 2.7	6.0 ± 0.00	0.511	0.197	0.049
concepts/39†	28.8 ± 8.2	24.1 ± 15.4	37.8 ± 1.81	0.925	0.007	0.003
memory/25‡	16.3 ± 6.8	11.2 ± 8.6	24.6 ± 1.26	0.240	0.003	<0.001
FCSRT						
Immediate recall/16	9.4 ± 6.2	8.2 ± 6.2	13.5 ± 2.07	0.381	0.325	0.034
3 free recall/48‡	10.7 ± 9.9	5.6 ± 7.5	26.0 ± 4.52	0.198	0.004	<0.001
3 total recall/48‡	23.0 ± 19.0	15.1 ± 16.0	43.4 ± 3.17	0.230	0.004	<0.001
Recognition/16‡	8.7 ± 8.2	7.3 ± 7.2	16.0 ± 0.00	0.427	0.002	<0.001
Free delayed recall/16‡	3.1 ± 3.0	1.8 ± 3.6	10.1 ± 2.42	0.244	0.001	<0.001
Total delayed recall/16‡	7.4 ± 6.0	4.9 ± 6.1	15.4 ± 0.70	0.533	0.001	<0.001
Intrusions†	4.3 ± 3.9	4.1 ± 6.9	0.0 ± 0.00	0.597	0.002	0.003
FAB/18‡	11.6 ± 4.3	8.3 ± 5.8	17 ± 0.82	0.204	0.001	0.001
Rey-Osterrieth/36†	23.6 ± 14.7	23.6 ± 14.6	35,8 ± 0.63	0.779	0.025	<0.001
DENO 30/30†	26.7 ± 4.6	20.8 ± 10.5	29.5 ± 0.71	0.187	0.069	0.003

Data are mean ± standard deviation. §Significant intergroup difference with Kruskal-Wallis ($p \leq 0.05$). †Significant intergroup difference with Kruskal-Wallis ($p \leq 0.01$). ‡Significant intergroup difference with Kruskal-Wallis ($p \leq 0.001$). p value: Significant differences between groups calculated by Mann-Whitney U test. AI, Intrathecal anti-*Borrelia* antibody index; DENO 30, oral naming of 30 items; FAB, Frontal Assessment Battery; FCSRT, Free and Cued Selective Reminding Test; MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination.

diagnosis in this second group (i.e., "neurodegenerative dementia and positive AI") was AD ($n=4$), AD and LBD ($n=3$, including one proven at autopsy), LBD ($n=1$), frontotemporal dementia ($n=3$), hippocampal sclerosis ($n=1$), and vascular dementia ($n=1$). The results of the CSF analysis (AD biomarkers, $n=8$), brain PET ($n=11$), and brain MRI were consistent with the diagnosis. Among these 13 patients, 2 patients had a history of neuroborreliosis: the patient with hippocampal sclerosis had sciatica and joints pain 10 years before cognitive impairment; one patient with AD had facial palsy 2 years before cognitive impairment. Two patients began simultaneously other neurological signs with cognitive impairment: the patient with vascular dementia had a sciatica; one patient with AD had a sixth nerve palsy. These 13 patients had concurrent positive AI and neurodegenerative disease. The characteristics of these patients, including the outcome of MMSE, and the results of cognitive tests administered at the start of the study to the two patient groups and the control group are shown in Table 1. The three groups were comparable in terms of age, gender, and educational level. There was no significant difference on any of the cognitive tests between the two patient groups. Nor was there any significant difference in any of the biological parameters, although the AI and CSF Lyme serology was three times higher for patients with neurodegenerative dementia (Table 2). The statistical differences found for the imagery parameters were: 1) the brain MRI results: there was more focal atrophy in the second group than in the first group (Table 2); and 2) the brain PET results: there was more frontal hypometabolism in the second group than in the first group (Table 2).

The final diagnosis of the 4 patients with positive Lyme serology but without any AI done was AD ($n=1$), FTLD ($n=1$), vascular dementia ($n=1$), and brain meningioma with epilepsy ($n=1$). The final diagnosis of the 14 patients with dementia with positive Lyme serology and negative AI was AD ($n=10$), AD and LBD ($n=1$), FTLD ($n=1$), vascular dementia ($n=1$), and progressive supranuclear palsy ($n=1$).

Table 2
Paraclinical characteristics of patients with dementia and positive AI. Group 1 includes patients with dementia and positive AI, without worsening after ceftriaxone. Group 2 includes patients with neurodegenerative dementia and positive AI, with worsening after ceftriaxone. The two differences between the two groups are the focal atrophy that was found in all neurodegenerative patients but two (one patient with Lewy body disease and one with vascular dementia), and the frontal hypometabolism, more frequent in the neurodegenerative group

	Neuroborreliosis and dementia ($n = 7$)/Group 1	Neurodegenerative dementia and positive AI ($n = 13$)/Group 2	p value
AI	3.2 (2.2)	9.4 (12.0)	0.341
Lyme serology IgG (U/l)	100.7 (52.6)	79.2 (75.9)	0.303
Western blot (No. bands)	7.3 (2.6)	6.9 (2.0)	0.798
Lyme serology IgG CSF (U/l)	47.3 (32.6)	147.1 (176.1)	0.074
Western blot CSF (No. Bands)	2.6 (1.0)	2.7 (1.9)	0.869
Protein in CSF (g/l)	0.52 (0.23)	0.47 (0.14)	0.905
White Cells CSF (/mm3)	0-1	0-1	1.00
FDG-PET hypometabolism (Number of patients)	5	12	
temporal	4	11	0.509
frontal	1	9	0.042
parietal	2	8	0.323
occipital	0	1	0.519
MRI	7	13	
(Number of patients)			
Vascular lesions	3	5	0.963
Focal atrophy	2	11	0.015
Diffuse cortical atrophy	1	3	0.648
Subcortical atrophy	1	4	0.429

AI, intrathecal anti-*Borrelia* antibody index; CSF, cerebrospinal fluid; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

DISCUSSION

Cognitive impairment in Lyme borreliosis exists not only with subtle neuropsychological symptoms but also with dementia. However, isolated (that means clinically without neurodegenerative dementia) Lyme dementia with progressive worsening after ceftriaxone does not appear to exist.

Thus, patients of the first group with Lyme dementia treated by ceftriaxone had a stable outcome or mild improvement but with sequelae. In this pure Lyme dementia group, there would appear to be various mechanisms which may contribute to cognitive impairment since two patients had vascular lesions, another had hydrocephalus. Four other patients had a predominantly hippocampal involvement clinically with storage deficit, but without or few focal atrophy, and without biological arguments for AD (CSF, for two patients). This tropism for the temporal lobe, and particularly the hippocampus, has already been reported in tertiary syphilis, with patients with memory impairment having more spirochetes in the hippocampus [10]. Memory impairment has also been described in 16% of European patients 30 months after they were treated for Lyme neuroborreliosis; such deficit could be due to sequelae after Lyme neuroborreliosis or insufficient therapy [11].

In the second group, patients with dementia and a positive AI worsened in the context of a neurodegenerative disease. These patients had criteria of neurodegenerative diseases (AD, DLB, AD and DLB, etc.) including CSF biological arguments for eight of them, and neuropathology for one. These patients deteriorated in 5 years, and the majority of them died or were obliged to be admitted in nursing home. The question of the adequate treatment is also questionable since there is no means to prove that the Lyme infection has been cured, even if we used 3 weeks of ceftriaxone.

The presence of *Borrelia* in the brain of a few patients with AD has previously been described [12]. Moreover late Lyme neuroborreliosis comprises meningoencephalitis and/or cerebrovascular infarcts characterized either by a strong lymphoplasmocytic infiltrates (infiltrative form) or by the atrophic form without infiltrates [1, 13]. This atrophic form was rarely described and it is usually associated with AD [14, 15]. We have shown here that the association between Borrelia and neurodegenerative diseases is not restricted to AD. The onset of such neurodegenerative diseases is known to be at least 14 to 20 years before dementia; these diseases can be diagnosed on clinical and cognitive basis, and lesions can be detected on CSF and amyloid PET imaging [16–18]. Here, the involvement of *Borrelia* in the central nervous system may

have revealed or worsened a neurodegenerative pathology (AD and/or LBD, FTLD, hippocampal sclerosis) that had been present for many years. Inflammation, particularly via microglia, is a known factor for clinical worsening of neurodegenerative pathologies [19, 20]. *Borrelia* induces inflammatory mediator production by microglia, and could thus worsen the clinical outcome of such neurodegenerative pathologies [21]. Further pathological studies are needed to better understand the association of Lyme neuroborreliosis and neurodegenerative diseases, and the potential role of inflammation.

The association of neuroborreliosis and dementia appears to be not so rare, since we found it in 20 out of 1,594 demented patients (1.25%). Among these 20 patients, we found 7 patients (0.44% of the patients with dementia) with a "pure" Lyme dementia. Our study was carried out in Alsace, a region of France with one of the highest rates of neuroborreliosis in the general population [22]. In endemic regions of Lyme borreliosis, it is important to systematically look for the diagnosis of Lyme dementia among demented patients, using Lyme serology. If serology is positive, CSF analysis with AI has to be done [4]. When the AI is positive, the treatment with ceftriaxone is of high importance since 7 of our patients have been stable or improved under this treatment.

It is noteworthy that AI is helpful when positive, but is not sufficiently sensitive (75%) that a negative test excludes the diagnosis of Lyme neuroborreliosis. Even if we used the most specific biomarker, we need more sensitive biomarkers to diagnose Lyme neuroborreliosis [4].

For only one patient, the diagnosis of neurodegenerative disease (for this case AD and DLB) was neuropathologically proven. However, for the other cases, clinical diagnostic criteria ensuring maximal specificity were used. In these conditions, the specificity of the clinical diagnosis compared to autopsy confirmed definite diagnosis for AD (using Dubois's criteria) is 93% [23], for DLB 98.3% [24], and for concomitant AD and DLB 96% [24]. Moreover, the patients were followed during a mean time of 5 years.

In conclusion, we have shown that "pure" Lyme dementia exists but does not worsen after specific treatment. Such etiological diagnosis has to be suspected in patients with brain MRI without or with few focal atrophy. In the case if dementia worsens in treated patients with a positive anti-*Borrelia* AI, clinicians should suspect the presence of a neurodegenerative disease, which may have been revealed by the involvement of *Borrelia* in the CNS. Further pathological studies are now needed to better understand the link between *Borrelia* and cognitive neurodegenerative diseases.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2197).

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