Risk factors for a non-favourable outcome after treated European Neuroborreliosis.

Randi Eikeland MD[1]

Åse Mygland MD PhD[2,3,4]

Karen Herlofson MD PhD[1]

Unn Ljøstad MD PhD[2]

[1]Department of Neurology, Sørlandet Hospital, Arendal, Norway

[2]Department of Neurology, Sørlandet Hospital, Kristiansand, Norway

[3]Institute of Clinical Medicine, University of Bergen, Bergen, Norway

[4]Department of Rehabilitation, Sørlandet Hospital, Kristiansand, Norway

Corresponding author:

Randi Eikeland

Department of Neurology,

Sørlandet Hospital HF, Arendal

Postbox 783

N-4809 Arendal

NORWAY

Telephone: +4790880246

Fax: +4737014010

E-Mail: randi.eikeland@sshf.no

Abstract

Aim: To identify risk factors for a non-favourable long term outcome with respect to Health Related Quality of Life (HRQoL) and fatigue after treated Lyme Neuroborreliosis (LNB).

Methods: We followed 50 LNB patients, and assessed outcome by the self-report questionnaires Short Form-36 (SF-36) and Fatigue Severity Scale (FSS) 30 months after treatment. We analyzed associations between these outcomes and demographical, clinical and laboratory data by univariate analyses and linear regression. Clinical status was assessed by a composite score based on subjective complaints and objective findings.

Results: Pre-treatment symptom duration > 6 weeks (B=-10.2, P=0.002) and non-complete recovery at 12 months (B=-5.6, P=0.033) were associated with lower scores in the SF-36 domain Physical Component Summary (R^2=0.59). Non-complete recovery at 4 months was associated with lower scores in the SF-36 domain Mental Component Summary (B=-8.9, P=0.01 (R^2= 0.37)). Pre-treatment symptom duration > 6 weeks (B=1.3, P= 0.028), high scores on the composite clinical score pre-treatment (B=0.1, P=0.019) and non-complete recovery at 12 months (B=1.7, P=0.001) were associated with higher FSS scores (R^2=0.70). No laboratory test results were associated with these outcomes.

Conclusions: Delayed treatment start, more symptoms and findings before and non-complete recovery at 4 and 12 months after treatment seem to predict a non-favourable outcome regarding HRQoL and fatigue 30 months after treated LNB. Age, gender, educational level involvement of the central nervous system pre-treatment, coexisting diseases and cerebrospinal fluid findings before treatment and during follow-up, were not associated whit long term HRQoL and fatigue.

INTRODUCTION

Lyme Neuroborreliosis (LNB) is usually effectively treated with antibiotics (1), but persisting complaints occur (2-4). Objective neurological findings after treated LNB are usually mild, but symptoms such as musculoskeletal pain, fatigue, cognitive deficits and reduced Health Related Quality of Life (HRQoL) are commonly reported (5-12). If such symptoms persist for more than 6 months after a documented episode of Lyme disease treated with a generally accepted antibiotic regime, the symptoms are of such a severity that they result in reduction in previous level of functions, and there are no other obvious explanations of the symptoms, the condition is proposed defined as Post-Lyme Disease Syndrome (PLDS) (13). Despite several theories such as persisting infection, autoimmunity, disturbances in the hormone axis, anxiety, depression and permanent tissue damage, the underlying pathology of PLDS is still unknown (14). Imaging of the brain does not show specific abnormalities (15,16) and persistent infection is unlikely as prolonged antibiotic treatment does not improve the outcome permanently and is not recommended (7,17-20).

It is important to increase our understanding of the remaining complaints after treated LNB, and one approach is to identify risk factors for a non-favorable outcome. It has been reported that fatigue, neurocognitive deficits, arthralgia and residual neurological findings are more common if the treatment is delayed (2,3,5,8,21), but to our knowledge predictors of HRQoL has not been addressed in European LNB studies until now.

The aim of our study was to identify possible clinical, demographical and laboratory factors associated with reduced HRQoL and fatigue 30 months after antibiotic treatment in a cohort of LNB patients.

MATERIAL AND METHODS

Patients and variables

From 2004 to 2008 we included 102 consecutive adult patients diagnosed with LNB in a multicenter treatment trial in Southern Norway (22). Out of these, 64 patients were recruited from two of the nine participating hospitals, covering the high endemic region of the Agder Counties. Fifty-seven of the 64 patients were included in the period May 2004-December 2007 and were all invited to participate in the current follow-up study. Fifty patients consented and were included. Neither the patients from the treatment trail who were not recruited to this follow-up study, nor the seven patients who were invited, but not included,

differed from the 50 included patients regarding treatment or severity of the disease before and 4 months after treatment. The patients were treated with doxycycline (n=26) or ceftriaxone (n=24), and were classified as having definite (n=34) or possible (n=16) LNB according to the European Foundation of Neurological Society diagnostic guidelines (23). Mean pre–treatment symptom duration was 9.2 weeks (Standard Deviation (SD) =19), 10 patients had pre-treatment duration of symptoms > 6 weeks, four of them >6 months (104, 76, 52 and 28 weeks, respectively).

Forty of the patients (80%) presented with partial or complete Bannwart syndrome (facial palsy (n=8), other cranial nerve affection (n=4), paresis arm/leg (n=8), radiculitis (n=20) with lymphocytic CSF pleocytosis). Other affections were plexopathy (n=1), findings indicating CNS involvement (myelitis (n=1), ataxia (n=2) or confusion (n=1)), and recent onset subjective symptoms (n=5) (headache, joint pain, myalgias, malaise, asthenia). All assessments took place in the Department of Neurology at Sørlandet Hospital. The participants filled in the questionnaires Short Form-36 (SF-36) and the Fatigue Severity Scale (FSS) 30 months (range 27-34) after treatment. We collected demographical, laboratory and clinical data pre-treatment and at 4, 12 and 30 months after treatment. The patients were asked about comorbidity and previous or current psychiatric problems. All patients underwent a lumbar puncture pre-treatment, 42 at 4 months, 33 at 12 months, and 29 at 30 months. We analyzed cell-count, protein level, anti-Borrelia antibodies and oligoclonal bands in the cerebrospinal fluids (CSF). CXCL-13 level was assessed in all patients pretreatment and 10 patients at 30 months. Based on a previous study we chose a CXCL-13 cut-off concentration of > 0 ng/g total CSF protein (24). Clinical outcome/burden of complaints was assessed by a composite clinical score (range 0-64) based on subjective reported complaints and clinical neurological findings (Table 1).

Table 1 Composite clinical score Lyme Neuroborreliosis patients. Previously published (22)

Subjective complaints (maximum score = 12)	Objective findings (maximum score = 52)
Malaise	Facial palsy *
Fatigue	Reduced hearing*
Pain	Vision loss l/r
Memory problems	Reduced sensibility in face*
Concentration difficulties	Paresis of eye muscles*
Paresthesia	Other cranial neuropathies
	Tremor
	Ataxia
	Nuchal rigidity
	Confusion
	Other CNS findings
	Radiculopathy truncus *
	Radiculopathy arm*
	Radiculopathy leg*
	Paresis arm*
	Paresis leg*

Clinical outcome score is the sum of subjective and objective findings. Each item is scored 0 = no, 1 = mild, 2 = severe (maximum total score 64). * Left and right sides scored separately.

Mean (SD) composite clinical scores pre-treatment, at 4 and 12 months were 8.3 (4.2), 2.7 (3.3) and 1.4 (0.9), respectively. A clinical score of > 1 was regarded as non-complete recovery. We reviewed individual hospital records to confirm the patients past medical history.

Outcome was measured by HRQoL in terms of Physical Component Summary (PCS) and Mental Component Summary (MCS) (range 0-100) on the SF -36 questionnaire, and by fatigue in terms of scores on the FSS questionnaire (range 0-7) 30 months after treatment. The mean PCS was 44 (SD=9), mean MCS was 49 (SD=11), and mean FSS score was 3.5 (SD=2.4) in our cohort (previously published (9)). Five of the patients fulfilled the diagnostic criteria of PLDS (13). Anti-Tick Borne Encephalitis (TBE) virus antibodies in serum were tested in all patients, three were positive for IgG, and none for IgM. We did not test for Anaplasma antibodies, but none of the participants had a clinical picture or a blood count suggestive of Anaplasma infection.

Ethics

All participants gave written informed consent. The study was approved by the Regional Committee for Medical Research Ethics in Southern Norway, and by the Norwegian Data Inspectorate.

This trial is a follow-up study on the treatment trial registered with ClinicalTrials.gov number NCT00138801

Statistical analysis

The statistical software SPSS version 16 was used for all analyses. For analyses of association between the continuous endpoints PCS, MCS and FSS and possible risk factors we did univariate analyses using Pearson's correlation for independent continuous variables and Student t-test for comparisons of means between groups. Education level was split into 3 levels and analyzed with Analysis of Variance (ANOVA). To be able to do a simultaneous assessment of multiple potential risk factors, all variables with P-values of 0.150 or less in the univariate analyses were included stepwise in a multiple linear regression model, one model for each of the three outcomes, PCS, MCS, and FSS. Because of missing data the CSF variables were analyzed separately. The results are presented with B-coefficient and with 95% confidence intervals (CI). P-values <0.05 were considered as statistical significant. We also report the R^2 (coefficient of determination) for each model. R^2 indicates how much of the variance in the outcome that is explained by the model.

RESULTS

Results of the univariate analyses of possible predictors of outcome are summarized in Table 2 and 3.

Table 2 Associations between categorical demographic, clinical and laboratory variables and Health Related Quality of Life and fatigue 30 months after treated Lyme Neuroborreliosis.

	PCS		**MCS**		**FSS**	
Variable (n)	Mean (SD)	P-value	Mean (SD)	P-value	Mean (SD)	P-value
Gender						
Male (27)	45.2 (11.1)	0.738	50.9 (11.5)	0.501	3.5 (2.0)	0.950
Female (21)	44.2 (8.2)		48.6 (11.9)		3.5 (2.0)	
Education: years after primary school*						
0-3 (24)	44.1 (7.9)	**0.030**	48.7 (14.2)	0.646	3.7(2.0)	0.667
4-6 (16)	41.2 (12.1)		52.3 (9.6)		3.5 (2.4)	
>7 (10)	51.6 7.4)		49.0 (7.7)		3.0 (1.3)	
Comorbidity pre-treatment						
Yes: (20)	39.9 (10.1)	**0.005**	48.5 (13.6)	0.576	4.4 (1.9)	**0.009**
No: (30)	47.9 (8.5)		50.8 (10.3)		2.9 (1.8)	
Treatment						
Ceftriaxone (26)	45.4 (10.9)	0,642	47.7 (12.6)	0.186	3.9 (1.9)	0.226
Doxycycline(24)	44.1 (9.0)		52.1 (10.3)		3.1 (2.1)	
Diagnostic accuracy						
Definite(34)	45.5 (8.8)	0.471	49.0 (12.0)	0.426	3.4 (2.0)	0.627
Possible (16)	43.3 (12.0)		51.8 (11.0)		3.7 (1.9)	
Pre-treatment CNS manifestations						
Yes: (4)	42.8 (4.8)	0.731	50.1 (18.3)	0.973	3.4 (2.5)	0.920
No: (46)	44.9 (10.2)		49.9 (11.4)		3.5 (2.0)	
Pre-treatment duration > 6 weeks						
Yes: (10)	34.6 (8.5)	**<0.001**	48.1 (13.2)	0.590	5.4 (1.9)	**<0.001**
No:(38)	47.4 (8.5)		50.4 (11.3)		3.0 (1.7)	
Recovery 4 months						
Yes: (18)	49.9 (6.4)	**0.006**	55.6 (4.7)	**0.001**	2.1 (1.9)	**<0.001**
No:(32)	41.9(10.4)		46.8 (13.1)		4.2 (1.2)	
Recovery 12 months						
Yes: (29)	48.6 (9.1)	**0.002**	51.7 (8.3)	0.233	2.5 (1.6)	**<0.001**
No:(21)	39.8 (8.7)		47.6 (14.9)		4.9 (1.6)	
Intrathecal BAB production 30 months						
Yes:(17)	44.1(10.1)	0.875	51.9 (9.1)	0.195	3.4 (2.1)	0.788
No: (11)	43.3 (11.8)		45.3 (16.5)		3.6 (2.1)	
CSF OCBs pre-treatment						
Yes: (24)	45.9 (8.9)	0.498	52.4 (9.3)	0.127	3.3 (1.7)	0.725
No:(13)	43.9 (7.4)		46.4 (13.5)		3.5 (2.3)	
CSF OCBs 30 months						
Yes: (12)	44.1(9.4)	0.888	44.7 (10.7)	0.101	4.0 (2.1)	0.906
No:(16)	43.5 (11.8)		52.8 (14.1)		3.9 (2.1)	

*The difference is between the group with 4-6 years education and the group with more than 7 years of education after primary school. SD= Standard Deviation, CI= Confidence Interval, PCS= Physical Composite Summary and MCS=Mental Component Summary of the Health Related Quality of Life questionnaire SF-36 (Short Form 36) 0- 100 (no problems), FSS =Fatigue Severity Scale (0 (no problems) -7), BAB= Borrelia Anti Bodies, OCB= Oligo Clonal Bands, CNS= Central Nervous System, CSF= Cerebro Spinal Fluid.

Table 3 Correlations of continuous demographic, clinical and laboratory variables with Health Related Quality of Life and fatigue 30 months after treated Lyme Neuroborreliosis

Variables*	Mean (SD)	PCS		MCS		FSS	
		Pearson`s Correlation Coefficient [95% CI]	P-value	Pearson`s Correlation Coefficient [95% CI]	P-value	Pearson`s correlation Coefficient [95% CI]	P-value
Age in years	56 (13)	-0.165 [-0.429-0.124]	0,262	0,029 [-0.257-0.31]	0.847	0.148 [-0.135-0.409]	0.305
Clinical score pre -treatment	8.3 (4.3)	-0.251 [-0.499-0.035]	0.086	-0.243 [-0.493-0.044]	0.096	0.449 [0.196-0.646]	**0.001**
CSF cell count pre-treatment (cells/mm^3)	187 (255)	-0.079 [-0.355-0.209]	0.594	-0.088 [-0.363-0.201]	0.552	0.158 [-0.125-0.417]	0.273
CSF cell count 4 months (cells/mm^3)	7.8 (11.4)	-0.031 [-0.339-0.283]	0.852	0.017 [-0.296-0.326]	0.981	0.046 [-0.261-0.345]	0.771
CSF cell count 12 months (cells/mm^3) (n=29)	3.72 (12.1)	0.011 [-0.363-0.382]	0.955	-0.333 [-0.628-0.045]	0.084	0.144 [-0.234-0.484]	0.458
CSF protein level pre-treatment (g/l)	1.22 (0,73)	0.088 [-0.201-0.363]	0.551	0.114 [-0.175-0.385]	0.441	-0.020 [-0.296-0.259]	0.891
CSF protein level 4 months (g/l) (n=42)	0.61 (0.24)	-0.017 [-0.326-0.296]	0.095	-0.086 [-0.387-0.231]	0.600	0.263 [-0.044-0.524]	0.093
CSF protein level 30 months (g/l) (n=29)	0.51 (0.20)	0.064 [-0.316-0.426]	0.747	-0.237 [-0.56-0.149]	0.224	0.134 [-0.244-0.477]	0.488
CSF CXCL 13 level pre-treatment (n=32)	5227 (11915)	-0.194 [-0.513-0.172]	0.296	-0.002[-0.356-0.352]	0.990	0.232 [-0.126-0.537]	0.202

As previously reported (9) we found that 14 of the patients had neurological findings 30 months after treatment: slight facial paresis (n=3), reduced hearing (n=1), reduced sense of feeling in the face (n=3), anisocoria (n=1), tremor (n=2), ataxia (n=2), nystagmus (n=2), radiculopathy (n=6) and slight arm/leg paresis (n=4) (ten had more than one finding). Twenty

patients had only subjective complaints, slight feeling of malaise (n=5), fatigue (n=15), pain (n=7), paraesthesias (n=7), memory (n=13) and concentration problems (n=9).
Ten patients reported previous or current psychiatric problems, two of them used anti-depressive medication at the time of follow-up because of a depressive disease. The other eight patients had minor psychiatric problems in their medical history. Mean Montgomery and Åsberg Depression Rating Scale (MADRS (range 0-60)) score was low, 3.1 (SD=4.9) (previously published (9)), and does not indicate depression.
A second tick-bite followed by an erythema migrans occurred in five patients in the period between LNB and 30 months follow-up, and all five received 14 days of per oral antibiotics. One patient had re-infection with LNB at follow up visit and was treated with intravenous ceftriaxone for 14 days.

Demographic and clinical factors

We found that pre-treatment symptom duration >6 weeks (B=-10.2, 95% CI -18.8- -6.7, P=0.002) and non-complete recovery at 12 months (B=-5.6, 95% CI -10.8- -0.5, P=0.033) were associated with a worse PCS score. The R^2 of 0.59 indicates that this final model explains 59% of the outcome variation. Non-complete recovery at 4 months (B=-8.9, 95% CI -15.5- -2.2, P=0.01) was associated with a worse MCS score. The R^2 of 0.37 indicates that this final model explains 37% of the outcome variation. Pre-treatment symptom duration >6 weeks (B=1.3, 95% CI 0.15-2.4, P=0.028), a higher clinical score pre-treatment (B=0.1, 95% CI 0.002-0.2, P=0.019) and non-complete recovery at 12 months (B=1.7, 95% CI 0.7-2.6, P=0.001) were associated with a worse FSS score. The R^2 of 0.70 indicates that this final model explains 70% of the outcome variation.

CSF findings

Due to missing data we analyzed the CSF variables separately. None of them reached a significance level of P= 0.05 or less in the univariate analyses or in the regression model.
Three patients (10%) had pleocytosis at 30 months follow-up (5, 6 and 66 white blood cell pr. mm^3 (cell count below 5 /mm^3 is regarded as normal)). The person with 66 cells had a tick-bite a few weeks before follow-up, and developed new symptoms (neck pain, joint pain, asthenia, balance problems).We regarded this as a reinfection with Borrelia, and the patient recovered after a second course of antibiotics.
Eight patients (28%) had slightly elevated CSF protein level at 30 months, 17 (61%) had intrathecal anti-Borrelia antibody production, and 12 (43%) had presence of CSF oligoclonal bands. The CSF CXCL-13 was elevated in 23/32 (72%) of the patients pre-treatment, and in 0/10 patients at 30 months (five of them reported remaining complaints).

DISCUSSION

We have previously found reduced HRQoL and more fatigue in Norwegian patients treated for LNB 30 months earlier as compared to matched controls (9). In the present study we wanted to identify risk factors for a non-favourable long term outcome with respect to HRQoL and fatigue. We found that pre-treatment symptom duration > 6 weeks and non-complete recovery at 4 or 12 months post-treatment were associated with reduced HRQoL, and that pre-treatment symptom duration more than 6 weeks, more complaints before treatment, and non-complete recovery 12 months after treatment were associated with a higher burden of fatigue 30 months after treatment. Demographic factors like age, gender and educational level and clinical factors like diagnostic accuracy, treatment option, involvement of the central nervous system, and coexisting diseases were not associated with HRQoL or fatigue burden in our cohort, neither were any of the assessed CSF findings pre-treatment or during follow-up like cell count, protein level, anti-Borrelia antibodies, oligoclonal bands or CXCL-13 levels.

The association between reduced HRQoL and non-complete recovery is not unexpected from a clinical point of view, as non-complete recovery in this present study was defined as a score of >1 on a composite clinical score based on subjective complains and objective findings. The association between a non-favorable long term HRQoL, prolonged time before antibiotic treatment and a higher burden of pre-treatment symptoms allow us to speculate if a more serious disease and longer duration of the disease before treatment can cause more permanent neural damage, like in other CNS infections (25,26). Poorer long-term outcome in patients with pre-treatment signs of CNS involvement and/or high degree of CSF inflammation might have underscored such a theory, but we did not find such an association in our cohort, maybe due to a small sample size. Suggested theories of underlying pathological mechanisms for a poor HRQoL and fatigue after LNB are autoimmunity (27) and ongoing persistent infection (28). We could not find laboratory support for any of these theories. None of our patients had elevated cell count at follow-up, except for one patient with a Borrelia re-infection. Some had slightly elevated CSF protein, presence of CSF oligoclonal bands and persistent intrathecal anti-Borrelia antibody production at follow-up, but these findings were not associated with a non-favorable outcome, neither were any CSF findings pre-treatment. Furthermore, normalized CSF CXCL-13 level at 30 months post-treatment argues against an ongoing Borrelia infection, at least in the 10 patient who had their CSF analyzed for CXCL-13. Overall, the CSF findings at follow-up in this study should be interpreted with caution due to

many missing data, and further research is recommended to elucidate laboratory signs of autoimmunity in patients with persistent long-term complaints after treated LNB. Another debated theory of remaining complaints is that some patients might be more vulnerable because of previous or current psychiatric conditions (29). We have shown in a previous study that patients in this cohort have the same amount of psychiatric comorbidity as a control group, and the MADRS scores were low (9).

We assessed the association between long-term HRQoL, fatigue and selected demographic, clinical and laboratory factors, but there may of course be other individual genetic and immunological factors which influence prognosis in different ways. Our statistical models explain between 40 to 70 % of the variation in the long-term outcome and there are probably several unknown factors involved. In addition to patient related factors, it is demonstrated in experimental models that different Borrelia burgdorferi species cause different clinical pictures, and it is possible that this can affect the long term outcome (30). It is also discussed if Anaplasma co-infection might worsen the outcome after Borrelia infection (31). We found no clinical or laboratory support of Anaplasma infection in our patient cohort.

Some previous studies have found delayed treatment to be predictive of a worse outcome (2,8,21). A US study including Quality of Life assessments found reduced HRQoL after Lyme disease as we did (5), others have not (20). A previous publication on this south Norwegian cohort showed that in addition to delayed treatment, female gender and high pre-treatment CSF cell count were associated with non-complete clinical recovery one year after treatment (3). We did not find gender or pre-treatment CSF cell count to be predictive of the outcome at 30 months regarding HRQoL or fatigue. Whether the patients were treated with oral doxycycline or intravenous ceftriaxone, or had a definite or possible LNB did also not influence on the long-term HRQoL or fatigue in this cohort. This is in coherence with the treatment study showing similar efficacy of these two treatments (22).

The strengths of our study are the prospective design, a well defined patient group, and use of validated and reliable questionnaires. The linear regression model allows us to do simultaneous assessment of multiple potential risk factors and to statistically explore their internal dependency of each other, and thus the analyses are more reliable than if only simple comparisons are made.

Weaknesses of our study are the many missing data regarding CSF analyses and the lack of a prospectively followed control group, but we have previously shown that there is a significant difference between patients with LNB and controls regarding HRQoL and fatigue 30 months after treatment in this cohort (9). We asked about current medication at the time of the follow-

up, but there is a possibility that we might have missed some information of interventions initiated by other doctors like pain killers or non-inflammatory medications.
There are still many unknown factors regarding potential risk factors of a non-favorable long-term outcome with respect to HRQoL and fatigue level after LNB, and our results are not applicable as prognostic hallmarks at an individual level. It seems reasonable though to avoid delay of antibiotic treatment, and to be aware of the possibility of fatigue after 30 months in those who have a more severe disease pre-treatment and do not recover completely after 12 months.

Conclusion

Pre-treatment symptom duration of LNB more than 6 weeks and non-complete recovery at 12 months seem to predict a reduced HRQoL 30 months after treatment. More clinical findings and symptoms before and non-complete recovery 12 months after treatment seem to predict a higher fatigue burden 30 months after treatment. No CSF findings pre-treatment were associated to reduced HRQoL or more fatigue, neither were CSF findings at follow-up, but the latter should be interpreted with caution due to missing data.

Contributors

RE was responsible for conception and design of the study and for data acquisition, analyses and interpretation. UL, ÅM and KH contributed to the conception and design of the study and to data interpretation. All authors revised and approved the final version of the manuscript.

Acknowledgements

We thank the Department of Research, Sørlandet hospital for support and Are Hugo Pripp, Unit for biostatistics and epidemiology, University Hospital of Oslo, for help with the statistics.

Funding This work was funded by the South-Eastern Health Authority of Norway.

Competing interests None.

Patient Consent Obtained.

Reference List

1. CERAR D, CERAR T, RUZIC-SALBJI E, WORMSER GP, STRLE F. Subjective symptoms after treatment of early Lyme disease. Am J Med 2010; **123**: 79-86.

2. BERGLUND J, STJERNBERG L, ORNSTEIN K, TYKESSON-JOELSSON K, WALTER H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infect Dis 2002; **34**: 421-5.

3. LJOSTAD U, MYGLAND A. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis; frequency, pattern and risk factors. Eur J Neurol 2009; **17**: 118-23.

4. VRETHEM M, HELLBLOM L, WIDLUND M et al. Chronic symptoms are common in patients with neuroborreliosis -a questionnaire follow-up study. Acta Neurol Scand 2002; **106**: 205-8.

5. SHADICK NA, PHILLIPS CB, LOGIGIAN EL et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med 1994; **121**: 560-7.

6. CARINS V, GODWIN J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 2005; **34**: 1340-5.

7. KRUPP LB, HYMAN LG, GRIMSON R et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology 2003; **60**: 1923-30.

8. BENKE T, GASSE T, HITTMAIR-DELAZER M, SCHMUTZHARD E. Lyme encephalopathy: long-term neuropsychological deficits years after acute neuroborreliosis. Acta Neurol Scand 1995; **91**: 353-7.

9. EIKELAND R, MYGLAND A, HERLOFSON K, LJOSTAD U. European neuroborreliosis: quality of life 30 months after treatment. Acta Neurol Scand 2011; **124(5)**: 349-54. doi:101111/j.1600-0404.2010.01482.x Epub 2011 Feb 9.

10. GAUDINO EA, COYLE PK, KRUPP LB. Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. Arch of Neurol 1997; **54**: 1372-6.

11. RAVDIN LD, HILTON E, PRIMEAU M, CLEMENTS C, BARR WB. Memory functioning in Lyme borreliosis. J Clin Psychiatry 1996; **57**: 282-6.

12. EIKELAND R, LJØSTAD U, MYGLAND A, HERLOFSON K, LOHAUGEN GC. European Neuroborreliosis: Neuropsychological findings 30 months post-treatment. Eur J Neurol 2011;oct15.doi:1111/j.1468-1331.2011.03563.x.Epub ahead of print

13. WORMSER GP, DATTWYLER RJ, SHARPIO ED et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006; **43**: 1089-134.

14. RUPPRECHT TA, KOEDEL U, FINGERLE V, PFISTER HW. The pathogenesis of lyme neuroborreliosis: from infection to inflammation. Mol Med 2008; **14**: 205-12.

15. AALTO A, SJOWALL J, DAVIDSSON L, FORSBERG P, SMEDBY O. Brain magnetic resonance imaging does not contribute to the diagnosis of chronic neuroborreliosis. Acta Radiol 2007; **48**: 755-62.

16. FALLON BA, LIPKIN RB, COBERA KM et al. Regional cerebral blood flow and metabolic rate in persistent Lyme encephalopathy. Archives of General Psychiatry 2009; **66**: 554-63.

17. FALLON BA, KEILP JG, CORBERA KM et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology 2008; **70**: 992-1003.

18. KLEMPNER MS, HU LT, EVANS J et al. A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001; **345**: 85-92.

19. KAPLAN RF, TREVINO RP, JOHNSON GM et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology 2003; **60**: 1916-22.

20. KEILP JG, COBERA K, SLAVOV I, TAYLOR MJ, SACKHEIM HA, FALLON BA. WAIS-III and WMS-III performance in chronic Lyme disease. J Int Neuropsychol Soc 2006; **12**: 119-29.

21. KRABBE NV, JENSEN TE, NIELSEN HI. Neuroborreliosis in North Jutland. Ugeskr Laeger 2008; **170**: 3420-24.

22. LJØSTAD U, SKOGVOLL E, EIKELAND R et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol 2008; **7**: 690-5.

23. MYGLAND A, LJOSTAD U, FINGERLE V, RUPPRECHT T, SCHMUTZHARD E, STEINER I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol 2010; **17**: 8-14.

24. LJOSTAD U, MYGLAND A. CSF B-lymphocyte chemoattractant (CXCL13) in the early diagnosis of acute Lyme neuroborreliosis. J Neurol 2008; **255**: 732-7.

25. HSU PC, YANG CC, YE JJ, HUANG PY, CHIANG PC, LEE MH. Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. J Microbiol Immunol and Infect 2010; **43**: 111-8.

26. POISSY J, WOLFF M, DEWILDE A et al. Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. Clin Microbiol Infect 2009 ;**15**: 560-4.

27. STEERE AC, COBURN J, GLICKSTEIN L. The emergence of Lyme disease. J Clin Invest 2004; **113**: 1093-101.

28. CAMERON DJ. Proof that chronic lyme disease exists. Interdiscip Perspect Infect Dis **2010**: 876450.

29. HASSETT AL, RADVANSKI DC, BUYSKE S, SAVAGE SV, SIGAL LH. Psychiatric Comorbidity and Other Psychological Factors in Patients with “chronic Lyme disease”. Am J Med 2009; **122**: 843-50.

30. PACNER AR, DALI D, BAI Y et al. Genotype determines phenotype in experimental Lyme borreliosis. Ann Neurol 2004; **56**: 361-70.

31. BELOGNIA EA. Epidemiology and impact of coinfections acquired from Ixodes ticks. Vector Borne Zoonotic Dis 2002; **2**: 265-73.