Cognitive function, fatigue and Fazekas score in patients with acute neuroborreliosis

1. Silje Andreassen[a,b]
2. Elisabeth Margrete Stokke Lindland[b,c,f]
3. Anne Marit Solheim[d,e]
4. Mona Kristiansen Beyer[b,f]
5. Unn Ljøstad[d,e]
6. Åse Mygland[d,e,g]
7. Åslaug Rudjord Lorentzen[d,i]
8. Harald Reiso[i]
9. Hanne Flinstad Harbo[b,h]
10. Gro Christine Christensen Løhaugen[a]
11. Randi Eikeland[a,i]

[a]Department of Pediatrics, Sørlandet Hospital Arendal, Postbox 416, 4604 Kristiansand ,Norway

[b]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[c]Department of Radiology, Sørlandet Hospital, Arendal Norway

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

[e]Department of Clinical Medicine, University of Bergen, Norway

[f]Division of Radiology and Nuclear Medicine Oslo University Hospital, Oslo, Norway

[g]Department of Habilitation, Sørlandet Hospital, Norway

[h]Department of Neurology, Oslo University Hospital, Norway

[i]The Norwegian National Advisory Unit on Tick-borne diseases, Norway

Corresponding author: Silje Andreassen, silje.andreassen@sshf.no

Abstract

Long-term cognitive problems and fatigue after adequately treated neuroborreliosis has caused uncertainty and debate among patients and health care workers for years. Despite several studies, the prevalence, cause and severity of such complaints are still not clarified. More knowledge about cognitive function, fatigue and MRI findings in the acute phase of neuroborreliosis could possibly contribute to clarification. In the current study, we therefore aimed to address this. Patients with well-characterized acute neuroborreliosis (n=72) and a matched control group (n=68) were screened with eight subtests from three different neuropsychological test batteries assessing attention, working memory and processing speed, and with Fatigue Severity Scale. Fazekas score was used to grade white matter hyperintensities on MRI. We found no differences in mean scores on the neuropsychological tests between the groups. The patient group reported significantly higher level of fatigue (Fatigue Severity Scale: 4.8 vs. 2.9, $p<.001$). There was no significant difference in Fazekas score between the groups. Neuroborreliosis does not seem to affect cognitive functions in the acute state of the disease, while fatigue is common.

Keywords:

Acute neuroborreliosis, cognitive function, fatigue, Fazekas

Introduction

In Europe, the nervous system is the main target if borreliosis disseminates, causing neuroborreliosis (NB). The most common manifestations of NB is meningoradiculitis affecting the cranial nerves and/or the spinal roots, causing pain, sensibility changes, paresis and cerebrospinal fluid (CSF) lymphocytic pleocytosis (Mygland et al., 2010). Most NB patients recover after antibiotic treatment, but 10 - 50 % report persistent health problems like fatigue, myalgia, cognitive problems and reduced quality of life (Eikeland et al., 2012; Eikeland et al., 2011; Knudtzen et al., 2017; Ljostad and Mygland, 2010; Westervelt and McCaffrey, 2002). Both the existence and severity of such long-term complaints have caused debate among clinicians and researches (Dersch et al., 2016). Until now, the majority of studies on cognitive function and fatigue related to NB have included patients in the post treatment phase. Since there are no European studies assessing cognitive functions in the

acute phase of neuroborreliosis, it is not known whether these symptoms exceed those of the general population.

Previous reports of MRI findings have reported non-specific involvement of brain and spinal cord, meningeal and nerve enhancement (Lindland et al., 2018). High intensity white matter hyperintensities were early on considered to be related to the infection (Fernandez et al., 1990; Halperin et al., 1989; Halperin et al., 1988; Morgen et al., 2001), but later studies suggest that these lesions are not typical for NB (Aalto et al., 2007; Agarwal and Sze, 2009). Fazekas scale was developed in an attempt to standardize the visual assessment of white matter hyperintensities seen on MRI (Fazekas et al., 1987). Today, Fazekas scale is used for describing the degree of white matter hyperintensities and is found to correlate with cognitive decline (Kynast et al., 2018; van der Flier et al., 2005; van Rooden et al., 2018).

The primary aim of our study was to assess cognitive function and the level of fatigue in patients with acute NB as compared to a healthy control group. Secondly, we aimed to compare the degree of white matter hyperintensities assessed by Fazekas score.

Methods and materials

Recruitment and participants

This study is part of an ongoing Norwegian multicenter treatment trial comparing two weeks and six weeks of doxycycline treatment for NB (Solheim et al., 2019). Patients aged ≥18 years with probable or definite NB according to the EFNS criteria (Mygland et al., 2010) were included in the treatment trial. Between November 2015 and December 2018, we invited patients included in the treatment trial at Sørlandet Hospital and Oslo University Hospital to participate in the present study of cognitive status, fatigue and MRI imaging in the acute phase. We also invited NB patients not participating in the treatment trial due to treatment with other antibiotic agents than doxycycline, if they fulfilled the other inclusion criteria. Seventy-three patients accepted the invitation. Out of 73 patients, 63 were recruited from the treatment trial, while nine patients had been treated with antibiotic agents other than doxycycline. One patient was excluded from the study, due to other diagnosis than NB. Out of the remaining 72 patients, two had contraindications for MRI (severe claustrophobia and intrathecal baclofen pump), but carried out neuropsychological testing.

Sixty-eight control persons matched for gender and age (+/- 2 years) were recruited by asking patients to bring a control person and through advertisement in a local newspaper. Out of 68 controls, four persons did not complete MRI, but carried out neuropsychological testing. All patients were examined with neuropsychological testing and MRI as soon as possible after diagnosis and treatment start, and all but seven patients carried out neuropsychological screening within 4 weeks after treatment started (median 18 days, range 2-38 days).

Other variables

We registered medication with fatigue as possible side-effect in the patient group and divided them into non-opioids, weak opioids, strong opioids, benzodiazepines, non-benzodiazepines (sleep aid), neuroleptica and antineuralgica (Table 1). Medication at baseline was registered in all but three patients.

Socioeconomic status (SES) was estimated based on Hollingshead index where education and occupational status are used to calculate a score from 1 to 5 (Hollingshead and Redlich, 1958).

Neuropsychological testing

Neuropsychological screening assessing attention/ working memory and processing speed included eight subtests. All tests in the protocol are validated and standardized. The tests were administered in a fixed order, and the same neuropsychologist performed all assessments. Neuropsychological scores -2 standard deviations (SD) below age adjusted scaled score were considered pathological.

In addition to objective testing, patients recruited from the treatment trial graded their experienced subjective memory/concentration problems from none to mild or serious.

Visual attention

Spatial Span forward and backward from Wechsler Memory Scale 3rd ed. (WMS-III) consists of a 10 block tapping board with blocks placed in random order. The examiner taps the blocks in a prearranged order, and the patient is supposed to copy this tapping pattern. The sequences increase gradually, until the patient is no longer able to keep track of it. In the second part of the test, the patient taps the sequence backwards. (Wechsler, 1997a).

In Color Word Interference Test Inhibition from Delis-Kaplan Executive Function System (D-KEFS), the patient must inhibit the response of reading, in order to name the dissonant ink color on the written color words. Raw score is the time used to complete the task. (Delis et al., 2001a).

Auditory attention

Digit Span forward and backward from Wechsler Adult Intelligence Scale 4th ed. (WAIS-IV) is a random sequence of numbers from 1 to 9 to be repeated by the participant. The sequence gradually increases until the patient is not able to repeat correctly any longer. In the backward condition, the patient is asked to repeat the examiner's number sequence backwards, starting with the last presented number (Wechsler, 2008a).

Processing speed

Color Word Interference Test Read consists of color words that the patient should read as fast and correctly as possible (Delis et al., 2001a).

Trail Making Test motor from Delis-Kaplan Executive Function System (D-KEFS) is a motor speed test. The patient is asked to follow a dotted line as fast as possible. Raw score is the time used to complete the task (Delis et al., 2001a).

Fatigue

Fatigue Severity Scale (Krupp et al., 1989) was used to identify level of fatigue in patients and controls. Fatigue Severity Scale (FSS) is translated into Norwegian and has been validated in the Norwegian population. A score of ≥5 is regarded as severe fatigue (Lerdal et al., 2005). All patients included from the treatment study were asked about subjective complaints regarding fatigue, and the problems were graded as none, mild or serious.

MRI

Imaging of the brain was performed in two centers with a Siemens Skyra 3T (Erlangen, Germany) with 64 channel head coil and a GE Discovery MR750 3T (Florence, USA) with 32 channel head coil. Fazekas score was used to grade white matter hyperintensities and this was performed by a neuroradiologist using the 3D FLAIR sequence (slice thickness 0,48 mm and 1.2 mm, respectively; FOV 245 and 256 mm; TR 5000 ms and 8000 ms; TE 389 and 90

ms; TI 1800 and 2071 ms). Fazekas scale ranges from zero to three. Fazekas 0, none or a single punctate WMH lesion; Fazekas 1, multiple punctate lesions; Fazekas 2, beginning confluence of lesions (bridging) and Fazekas 3, large confluent lesions. Fazekas grade 1 is considered normal in elderly. Fazekas grade 2 is considered normal in individuals above 71 years old, whereas grade 3 is considered pathological (Vernooij and Smits, 2012). Other imaging findings related to the infection or of incidental character were also noted.

Statistical analysis

The statistical software SPSS Statistics 25 was used for all analyses. We used independent samples *t*-test and Mann-Whitney U to compare mean scores in the two groups. To adjust for multiple comparison we used Bonferroni correction (adjusted *p*-value =.005). Chi-square test was used to compare proportions. Differences between groups are based upon raw scores. Spearman rho was used to correlate neuropsychological tests results with FSS since data did not meet the criteria for using parametric correlation. To determine whether a subject had a pathological low score, we used age-corrected scaled scores based on normative data. Missing data on the neuropsychological tests occurred randomly. Two patients and one control person missed spatial span, and two different patients missed one subtest each; Color Word Interference and Trail Making Test. One patient did not fill out Fatigue Severity Scale. In the analysis, missing data were handled by using pairwise deletion.

Ethics

The study is part of the BorrSci project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties) and is approved by the Norwegian Regional Committee for Medical and Health Research Ethics, the South-Eastern region (2015/1031 and 2015/1588) as well as through local routines at Sørlandet Hospital and Oslo University Hospital. All participants gave written informed consent.

Table 1

Results

Demographic and clinical data are presented in table 1. The NB patient- and control groups are similar with respect to age, gender distribution, and SES. Mean neuropsychological test

results, scores on FSS and Fazekas are presented in table 2. There were no significant differences in neuropsychological mean scores between the groups. Thirteen patients and 10 control persons had a pathological score, defined as -2 SD on at least one subtest. The difference was not significant (p=.759). The 63 patients recruited from the treatment trial were asked to grade their subjective experience of cognitive problems at inclusion as none, mild or serious. Out of 61 responders, 40 patients reported no problems, 19 mild and two patients reported serious problems. We divided NB patients into two subgroups, definite NB (n=59) and possible NB (n=13). Patients with possible NB had subacute neurological symptoms suspicious of NB and elevated leucocytes in the spinal fluid (> 5), but not detectable intrathecal Bb antibody production (negative index). All the patients with possible NB had meningoradiculitis (10/13) and/or cranial neuritis (5/13), and 12 had concurrent malaise, muscle/joint pain, fatigue and headache. When comparing patients with definite and possible NB, we found no significant differences between the groups on neuropsychological test results, FSS or Fazekas score.

Patients with NB reported higher level of fatigue than the control group. Out of 61 responders, 13 reported no subjective experience of fatigue, 16 mild and 32 serious. Patients who filled out FSS (71 out of 72) had higher score than controls 4.8 vs 2.9 (p< .001), and more patients (36/71(51 %)) than controls (7/68(10 %)) reported severe fatigue defined as FSS score ≥5 (p=<.001).
There were no significant correlations between FSS and neuropsychological tests in the patient group after Bonferroni correction.

Table 2

We found no difference in Fazekas score between the groups. Median Fazekas score in both groups was one. Other imaging abnormalities were cranial neuritis in about half of the patients (will be reported in a separate study), as well as inflammatory changes of meninges, brain and/or spinal cord in four patients. Seven patients and six control subjects had

incidental findings on MRI. There were no significant correlation between patients with neuropsychological scores below -2 SD and Fazekas score or FSS.

Discussion:

One third of the patients with acute NB reported subjective memory and/ or concentration problems before treatment, yet we found no difference in cognitive status between patients and healthy control persons. In terms of fatigue, the patient group had a significant higher score on fatigue severity scale (FSS). There was no difference in white matter hyperintensities on MRI as assessed with Fazekas score between patients and controls. Regarding cognitive function in NB patients, the most frequent and persisting findings are reduced verbal memory and especially deficits in list-learning tasks (Westervelt and McCaffrey, 2002). Reduction in processing speed (Keilp et al., 2006; Pollina et al., 1999) and attention/working memory (Bujak et al., 1996; Eikeland et al., 2012; Keilp et al., 2006) have also been reported. These studies have assessed cognitive function several months to years after treatment. There is only one study assessing cognitive function in the acute phase of borreliosis. This study assessed cognitive function and subjective health problems in patients with erythema migrans and concurrent flu-like symptoms (Bechtold et al., 2017). They found no differences between patients and controls in attention, processing speed, mental flexibility or verbal learning. The study is, however, not completely comparable to ours. The control group was small and it is uncertain if any of the patients had NB in addition to erythema migrans. Further, studies including patients with localized borreliosis show that they do not have persisting symptoms that exceed those of the general population (Eliassen et al., 2017). Patients with disseminated NB on the other hand, seem more susceptible to experience cognitive problems and fatigue (Eikeland et al., 2011). Consequently, this current study is the first study of cognitive function in the acute phase of NB.

The patients in our sample were asked to grade their subjective symptoms when treatment started, while the NP testing was carried out later (median 18 days). Patients tend to improve rapidly after starting up antibiotic treatment (Ljostad et al., 2008). We were interested in whether any of the deficits reported in long-term studies could be identified in the early phase of the disease. Although we did not include tests on long-term memory, we

included tests on working memory in our protocol. Working memory is a theoretical model and refers to our ability to keep attention to information over a short period of time, and at same time being able to manipulate this information (Baddeley et al., 2019). Working memory is regarded as important both in learning as well as in storage retrieval (Schurgin, 2018).

Discrepancies between subjective cognitive complaints and objective findings are known, and have been demonstrated in various patient samples (French et al., 2014; Pranckeviciene et al., 2017; Zlatar et al., 2018). Self-reported cognitive problems may be related to psychological distress rather than actual cognitive decline (French et al., 2014). One hypothesis has been that fatigue is causing the cognitive deficits found in patients with post treatment symptoms. Our findings do not support this as we found no association between fatigue and neuropsychological test results. These results are in line with findings from other studies, suggesting no correlation between fatigue and cognitive function in patients measured two years after treatment (Eikeland et al., 2012).

Neither neuropsychological testing nor Fazekas score for white matter hyperintensities showed any difference between the groups. Previous research on structural changes in NB have shown varied results regarding white matter changes. Agarwal & Sze (2009) found white matter lesions in seven out of 66 patients, but also in six out of 50 healthy controls. This could suggest findings due to aging and vascular changes, rather than the infection itself. Studies including MRI and neuropsychological testing of NB patients are scarce in numbers and hampered with a low sample size. In a sample of 23 patients with PLDS, Morgen et.al (2001) found subcortical lesions in half of the patient group. Thirteen patients were assessed with objective tests of memory and six of them had memory deficits. There was no association between memory deficits and subcortical lesions. The range of symptoms in NB is wide, and also findings on MRI are variable and non-specific. The connection between NB infection and white matter hyperintensities is uncertain (Lindland et al., 2018).

The strengths of our study are the large sample size, well-characterized NB patients diagnosed based on the possible/ definite case definition recommended by the EFNS guidelines (Mygland et al., 2010), and an age- and gender matched control group.

A potential limitation of our study is the choice of neuropsychological tests. A limited number of tests was chosen because the patients were in an acute phase of the disease, were pain, malaise and fatigue were part of the clinical picture. We considered an extensive neuropsychological assessment to be overwhelming for the patients in this stage. We chose to assess attention, working memory and processing speed, functions that are important to learn and store new information. We cannot rule out that functions like executive functions or other processes involved in memory consolidation and retrieval are affected. Another possibility could be that our choice of neuropsychological tests were insufficient and did not capture the spectrum of attention and processing speed. Finally, although we tested the patients soon after antibiotic treatment initiation, patients who improved rapidly might also have improved their cognitive function. We cannot rule out the possibility that neuropsychological scores in the patient group might have been lower if they had been tested the same day the treatment started. Regarding MRI measures, Fazekas score may not be sensitive enough to evaluate white matter involvement in NB patients, and other measures would be more suitable for this patient group.

Conclusion

Patients report subjective cognitive problems and fatigue in the acute phase of neuroborreliosis. We did not find any differences in cognitive function or Fazekas MRI score between patients with acute neuroborreliosis and matched controls, but patients had higher level of fatigue than controls.

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407 Table 1. Demographic data and socioeconomic status in patients and controls.
408 Neuroborreliosis classification, clinical data and potential fatigue inducing medication in the
409 patient group.

	NB-treated patients (n=72)	Controls (n=68)
Mean age (range)	57.3 (20-81)	57.8 (25-81)
Gender (%)		
Male	36 (50)	32 (47)

Female	36 (50)	36 (53)
Marital Status (%)		
Married	42 (58.3)	43 (63.2)
Registered partner	10 (13.9)	8 (11.8)
Divorced	4 (5.6)	7 (10.3)
Widow	2 (2.8)	5 (7.4)
Unmarried	10 (13.9)	4 (5.9)
No data	4 (5.6)	1 (1.5)
SES (mean)	3.4	3.6
Definite NB (%)	59 (81.9)	*
Possible NB (%)	13 (18.1)	*
Median CSF cells/mm spinal fluid (range)	122 (7-752)	*
Intrathecal *Bb* antibody production (%)	59 (81.9)	*
Days since treatment start (range)	18 (2-38)	*
Medication (%)		
Non-opioids	21 (29.2)	*
Weak opioids	15 (20.8)	*
Strong opioids	9 (12.5)	*
Benzodiazepines	1 (1.4)	*
Non-benzodiazepines sleep aid	4 (5.6)	*
Neuroleptica	3 (4.2)	*
Antineuralgica	23 (31.9)	*

Abbreviations: SES, socioeconomic status; NB, neuroborreliosis; CSF, cerebrospinal fluid; Bb, *Borrelia burgdorferi*

Table 2. Neuropsychological test results, FSS and Fazekas score in patients with acute neuroborreliosis (n=72) and controls (n=68). Numbers are raw scores (standard deviation).

Function	Measure	Patients (n=72)	Controls (n=68)	*p*-values
Attention	Digit Span Forward	8.4 (1.9)	8.9 (2.2)	0.209
	Digit Span Backward	7.5 (1.9)	8.0 (1.9)	0.117
	Spatial Span forward	7.1 (1.7)	7.1 (1.7)	0.986
	Spatial Span Backward	6.6 (1.9)	6.6 (2,0)	0.884
	Spatial Span total	13.7 (3.1)	13.7 (3.3)	0.980
	Color Word Inhibition	60.8 (19)	59.3 (15.6)	0.593
Processing speed	Color Word Read	22.4 (5.9)	21.2 (3.3)	0.148

	TMT 5	28.3 (18.1)	24.2 (8.7)	0.086
Fatigue	FSS	4.8 (1.8)	2.9 (1.4)	<0.001*
WMHs	Fazekas (median (range))	1 (0-3)	1 (0-2)	0.287

418 Abbreviations: TMT, Trail Making Test; FSS, Fatigue Severity Scale and WMHs, white matter
419 hyperintensities. *Level of significance after Bonferroni correction is p<0.005
420