Author's response to reviews

Title: Severe course of Lyme neuroborreliosis in an HIV-1 positive patient; case report and review of the literature.

Authors:

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Author's response to reviews: see over
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Dear Editor and Reviewers,

Thank you for reviewing our manuscript. We have read your comments well and taken them to heart. We adjusted the manuscript to the journal style. Below are our point to point answers to the concerns of the reviewers.

Reviewer 1

1. Question: Peripheral Lyme serology and Western blot were said to be positive. What was the value of the C6 ELISA and what bands were present on Western blot? How did this compare to the European consensus criteria? Was a Western blot performed on CSF? Were other bands present?
   Answer: We added the data to the article: The C6 LI-value was 10.6 (OD was 3.6) (Immunetics QuickELISA), Immunoblot was IgM negative, IgG positive for p100/83, VlsE, p41(i), p39, DbpA, but not for OspC and OspA (RecomBlot, Mikrogen). This blot was positive according to European guidelines (Robertson et al., 2000, J. Clin. Microbiol, 38, 2097-2102). Blot performed on the CSF did not show additional bands.

2. Q: Which PCR assay was used for OspA detection and what is that assay’s sensitivity and specificity?
   A: We performed our in house OspA PCR as previously described with 50% sensitivity and 100% specificity (Gooskens et al, Evaluation of an internally controlled real-time PCR targeting the OspA gene for detection of Borrelia burgdorferi sensu lato DNA in cerebrospinal fluid, Clinical microbiology and Infection, 2006 vol 12:9 pag 894-900). The reference for this PCR is included in the paper.

3. Q: The authors refer to this patient as having “chronic LNB”. In the European literature the term “late LNB” is usually defined as 6 months or more of evident disease. This patient’s symptoms were of 3 months duration. I am not aware of a good definition of “chronic LNB” but that term would not seem appropriate here.
   A: We agreed with the reviewer that chronic neuroborreliosis is an inappropriate term and adjusted the manuscript accordingly.
   For clarification: in the EFSN guidelines the late and chronic neuroborreliosis terms are used for the same patient group. In the EUCALB guidelines late is not mentioned and chronic neuroborreliosis is defined as longstanding encephalitis /encephalomyelitis/ meningoencephalitis/ radiculomyelitis. The dutch CBO guideline refers to the EUCALB guideline. The patient had a meningoencephalitis for three months. To evade further confusion in the current version we used meningoencephalitis.

4. Q: The patient was treated for 1 month “according to national guidelines”. Although this is common and acceptable practice, current EFNS Guidelines actually recommend 3 weeks.
   A: We clarified in the paper that the national guideline has the same treatment regimen as the EUCALB guideline. It is correct that the EFNS guideline advises 3 weeks of treatment. The EUCALB guideline and the dutch CBO guideline
prescribe 4 weeks of IV treatment in the case of a meningoencephalitis. We operated according to the EUCALB/CBO guideline.

5. Q: Intrathecal antibody production was not evident on repeat CSF exam. This is actually somewhat surprising – how long after treatment was this follow up LP? A: We clarified this in the paper. The first follow up lumbar puncture was performed roughly 2 months after treatment. Antibodies against *B. burgdorferi* were still present intrathecally, but at much lower rates than the pre-treatment lumbar puncture. AI was barely negative. Although it is common that the antibody index can stay positive for very long periods, it is not uncommon that the AI can become negative as soon as two weeks after treatment (Ljostad, Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis, European Journal of Neurology 2007, 14;873-876).

6. Q: The authors repeatedly assert the patient showed little improvement. However at the onset of treatment she was confined to a wheelchair and at follow-up she was ambulatory (cane) with 3-4/5 strength in the lower extremities. A: We agree with the reviewer that 'little improvement' was not a poor description and altered the manuscript accordingly. It is correct that after starting the treatment the patient was confined to a wheelchair. Strength improved after treatment, but the altered gait persisted. Invalidity was still very high and after treatment she performed about as well as at presentation.

7. Q: The authors attribute the failure to improve to the patient’s immunodeficiency. However, in patients with this type of parenchymal inflammatory brain disease – due to LNB or any other cause - the ability to recover is dictated by the severity of their deficits at the time treatment is initiated. Given that she was wheelchair-confined, the expectation for recovery would be limited, regardless of her immune status or the cause of the brain inflammation. Since this patient was minimally immunocompromised I would consider this assertion unproven. A: We clarified our point of view in the paper. We agree with the reviewer that outcome of treatment is dictated by the severity at the start of treatment. However the severity of primary presentation and severity of the sequelae as seen in our patient is rare. Furthermore, persistent sequelae are seen more often in patients in whom treatment is delayed for years, not for just three months (Shadick et al Ann intern Med, 1994 Oct 15; 121 (8); 560-570). We do contribute the quickly progressive disease to the HIV infection, as is also seen in *T. pallidum* infections. Patients with HIV and near normal CD4 cell counts still have an altered immune response. We added the suggestion that the altered CXCL13/CXCR5 receptor complex, also in HIV patients that do not have AIDS, and altered inefficient B-cell response might contribute to a more rapidly progressive infection (Widney DP, Breen EC, Boscardin WJ, Kitchen SG, Alcantar JM, Smith JB et al.: Serum levels of the homeostatic B cell chemokine, CXCL13, are elevated during HIV infection. J Interferon Cytokine Res 2005, 25: 702-706).

Reviewer 2

1. Q: The authors report negative results for various HIV-related coinfections, but ironically they fail to mention coinfections with tickborne organisms such as Babesia, Anaplasma, Ehrlichia and Bartonella. Infection with all of these organisms has been reported in HIV patients (Vyas et al, Clin Infect Dis.

A: It is correct that we did not test for these organisms. We concluded it was highly unlikely, because of clinical and epidemiological data, that a co infection with said organisms played a role in this case. This patient had no travel history. Anaplasmosis has described only once in the east of the Netherlands (van Dobbenburgh et al, NEJM 1999, 340: 1214-1216). Human cases of babesiosis and ehrlichiosis have so far never been reported in the Netherlands. At presentation the patient was afebrile and no petechiae were seen, which also makes these co-infections less likely. In the Netherlands bartonella infections are prevalent, though so far no human cases are described by tick inoculation. Additional PCR and serology will be performed on the CSF and serum of this patient to exclude bartonella infection. Clinically we find this possibility unlikely.

2. Q: The authors state that persistent sequelae are "a very rare complication of LNB". To say the least, this statement is controversial. Studies in adults and children have shown persistent neurocognitive symptoms in a significant number of patients with treated LNB (Logigian et al, N Engl J Med. 1990;323:1438-44; Shadick et al, Ann Intern Med. 1994;121:560-7; McAuliffe et al, Appl Neuropsychol. 2008;15:208-19). Thus the persistent symptoms seen in the patient described by the authors may not be as uncommon as they assume.

A: We agree with the reviewer that mild sequelae are not "very rare". The reviewer includes articles which describe cognitive impairment (memory deficits, fatigue), paresthesia and arthralgias. Sequelae of this magnitude are rare after treatment, especially if treatment was not delayed. In this case only three months after the start of complaints the sequelae were already this severe (Logigian et al, N Engl J Med. 1990;323:1438-44; Bagger-Sjöbäck D, Otol Neurotol. 2005 Jul;26(4):790-5; Berglund J Scand J Infect Dis. 2002;34(6):421-5, Skogman BH Pediatr Infect Dis J. 2008 Dec;27(12):1089-94). We adjusted the article to make the statement clear and further clarify the complaints the patient suffered from.

3. Q: Table 1 shows clinical data from the published reports of patients with LNB and HIV disease. Several modifications should be made to the Table: (a) Patient 1 had a CD4 T-cell count of 386/ul according to Table 1 in Reference 1. (b) It would be better to show the normal range for CD4 T-cells in each study rather than the T-cell ratio, which is meaningless. (c) In addition to antiretroviral therapy, use or non-use of antibiotic prophylaxis should be listed for each patient (see #4 below). And (d) the V should be changed to F. In terms of the discussion of this Table, it is noteworthy that only Patient 3 met CDC criteria for AIDS based on a CD4 T-cell count under 200/ul. Thus LNB occurred in relatively healthy HIV patients, possibly explaining the relatively good outcome in these cases.
A: We have altered the table and added and removed all suggestions as proposed by the reviewer.

4. Q: The reason that Bb infection is not described more often in HIV disease is unclear. Several explanations have been advanced, and the authors may wish to elaborate on them. The standard explanations are that the two infections occur in distinct populations, and that Bb infection may be masked by similar symptoms of HIV disease. These explanations are extremely weak. A more intriguing possibility is that prophylactic antibiotics given over the long term in HIV patients may prevent Bb infection, or that antiretroviral therapy itself may prevent Lyme disease. These possibilities raise issues about treatment of Bb that are important to consider. Along these lines, was the patient taking prophylactic antibiotics? If not, this should be clearly stated in the Case Report section.
A: We added discussion about this point to the manuscript. Our patient, as the other described HIV patients, did not use antibiotic prophylaxis. The suggestion done by the reviewer is very interesting. However in terms of antibiotic prophylaxis the usual practice is prescribing cotrimoxazole to patients at risk of developing PCP. Cotrimoxazole has no activity against B. burgdorferi, only a slight impairment of growth after days at supraphysiologic levels in vitro (Baradaran-Dilmaghani R, Stanek G: In vitro susceptibility of thirty Borrelia strains from various sources against eight antimicrobial chemotherapeutics. Infection 1996, 24: 60-63). We have no data that suggests that antiretroviral therapy has anti-borrelia activity. Three out of the five patients were using anti-retroviral therapy, this does not support a positive nor a negative effect.

Minor comments:
1. Q: Was strain typing done for the Bb?  
   A: We did not culture the strain, which complicates typing.
2. A: The sentence "Oligoclonal bands for B-cells were detected" was altered to; “By isoelectric focussing oligoclonal IgG was detected intrathecally”

We sincerely hope we have responded to the reviewers concerns adequately. Any questions that remain we are happy to answer,

Sincerely,

Nathalie van Burgel