Author's response to reviews

Title: Transverse Myelitis and acute HIV infection: a case report

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Version: 4 Date: 2 March 2014

Author's response to reviews: see over
Letter to the Editor

We would like to thank the Editor and the Referees for their comments and suggestions, as we believe they will further improve this case report.

**Referee 1:**

1. **Is it possible to report the specific proteins which turned out positive in the indeterminate Inno-Lia test?** We would expect that the repeated test, although still indeterminate, could have more positive bands, thus confirming the diagnosis of acute HIV seroconversion. The same request for the wife of the patient.

   A: Three different Inno-Lia tests were performed on this patient. The first one was positive for gp41, as well as the second, performed 2 weeks later. The third Inno-Lia test, performed 3 months later, was positive for p17, p24, p31, gp41 and gp120. This information has been included and corrected in the manuscript. We have excluded all information regarding the patient’s wife, as was suggested by reviewer 2.

2. **Was the diagnosis of HIV-related acute transverse myelitis a diagnosis of exclusion?** It seems so, but it should be written overtly.

   A: It was indeed a diagnosis of exclusion. We have rewritten and clarified this aspect in the manuscript.

3. **Why was the diagnosis of post-infectious myelitis following acute gastroenteritis excluded?**

   A: Although rare, neurological manifestations (including acute transverse myelitis) have been associated with *Campylobacter jejuni* diarrhea. Gastrointestinal symptoms had resolved by the time our patient was admitted, so no stool specimen for microbiology was obtained. Serology for *C. jejuni* (IgG) might be helpful when evaluating a patient assumed to have a post-infectious diarrhea neurologic disease, namely presenting as Guillain-Barré syndrome. Nevertheless, determining the significance of a positive serological result is difficult, since it cannot establish the time of infection with accuracy.

   On the other hand, our patient had a gastroenteritis episode suggestive of a toxin-mediated disease. He and his room-mates had shared a meal and subsequently all developed symptoms in less than 24 hours, with rapid clinical resolution. Although not impossible, campylobacter gastroenteritis is less plausible in this context.

   Finally, we identified a more likely, albeit rare, cause for acute transverse myelitis, namely acute HIV infection. He had evidence of both acute HIV-1 infection, according to the serological evolution, and central nervous system involvement, with HIV-1 replication in the cerebrospinal fluid.
4. Would it be possible to have in the paper also the magnetic resonance images?
A: We have included a magnetic resonance image in the manuscript.

Referee 2:

Major Compulsory Revisions.

1. "Peripheral neuropathy may occur in primary HIV infection but central nervous system disorders in this setting are rare" – please correct: aseptic meningitis is among the most common manifestations of HIV seroconversion.
A: We have replaced this sentence for “Neurologic symptoms may occur in acute HIV infection but myelopathy in this setting is rare”.

2. “In tropical areas the differential diagnosis of neurological disorders is particularly difficult, as a broader range of infectious and non infectious causes need to be considered” – reference? if his statement is not evidence based, please remove.
A: It is common medical knowledge that a number of infectious diseases with neurological manifestations are more prevalent in tropical areas, including Angola. A quick survey on WHO or CDC statistics reveals that Angola still had, at the time of this clinical case, reports of poliomyelitis, tetanus, schistosomiasis, sleeping-sickness and rabies, to name a few, all of which have been eradicated or are highly uncommon in Portugal. HIV/AIDS, syphilis, rickettsiosis and borreliosis, although present in Portugal, are significantly less prevalent than in Angola. We believe that referencing data for all of these pathologies is not relevant. Nevertheless, we have rephrased the sentence to: “In tropical areas, differential diagnosis of neurological disorders is particularly difficult, as a broad range of infectious causes needs to be considered”.

3. "Magnetic Resonance Imaging (MRI) of the brain was normal, but MRI of the medulla showed extensive hyperintense signal in the long TR sequence throughout C4 to T11, especially in the posterior columns, suggesting inflammatory/infectious aetiology” - please include the MRI in the manuscript.
A: We have included a magnetic resonance image in the manuscript.
4. Didn’t the authors considered neurosarcoidosis (the patient had cutaneous, pulmonary manifestations, and myelitis) and tested the angiotensin-converting enzyme levels?

A: We have not considered neurosarcoidosis at all. Our patient’s cutaneous manifestations consisted of three red spotted (and later on necrotic) lesions on the abdomen, highly suggestive of animal bite. This is not a usual skin manifestation of sarcoidosis, neither in its appearance nor in its location. Regarding pulmonary manifestations, though our patient did present dyspnea and dry cough, chest roentgenography was normal, a feature which is highly uncharacteristic of sarcoidosis. All things considered, sarcoidosis was ruled out as a possible diagnosis for this patient.

5. The discussion is centered in the differential diagnosis of transverse myelitis. There are several and comprehensive updated revisions on the topic. I suggest to eliminate or reduce dramatically the discussion on the differential diagnosis of transverse myelitis – this is not the main message of the case. Instead, the authors should discuss:

- What are the possible mechanisms of transverse myelitis during acute HIV infection (considering the good recover without HAART).
- What are the advantages of starting HAART in acute HIV infection with neurological involvement

A: We do not fully agree with the reviewer. Although a thorough review of the aetiology of transverse myelitis may be beyond the scope of this case report, the main challenge, utility and educational value of this clinical case is the differential diagnosis workup in a patient with no apparent risk factors for HIV infection, as was duly noted by reviewer 1. We believe this to be one of the main messages of the case, alongside with this clinical presentation of acute HIV infection.

6. Misdiagnosis of HIV acute infection is common. Virtually any neurological manifestation can occur during HIV acute seroconversion. The authors should briefly discuss what clinical, laboratory hints are important to consider the diagnosis of HIV seroconversion.

A: We have included a brief description of the classic symptomatic acute HIV infection. Our patient did not present those classic manifestations.

7. Considering rarity of acute myelitis and the identification of the Hospital where the patient was treated, the manuscript contains a set information that in
combination potentially compromise the anonymity of the patient - in particular the information about the travel to Africa/Luanda. Instead of information about traveling to Africa/Luanda (which is not a risk factor for HIV infection), the authors should deny or affirm unprotected sex, use of intravenous drugs per example.

A: According to the Portuguese Embassy in Luanda, Angola, over 20,000 Portuguese citizens entered the country in 2009 and over 110,000 Portuguese citizens resided in Angola in 2012. We evaluate hundreds of travelers in pre-travel consultation in our Hospital, of whom about one third are destined to Angola. Furthermore, several patients return from Angola to be evaluated in our Hospital in the setting of acute illness. We decline to omit information about residing in an African country for 10 months, as the clinical picture started in Angola and we believe this was an important epidemiologic feature that contributed to a wider and interesting differential diagnosis workup. Nevertheless, we will omit information regarding residency in Luanda. In this way, we believe that patient anonymity is fully guaranteed.

Denial of unprotected sex, use of intravenous drugs and other risk factors for HIV infection had already been included in the manuscript.

Minor Essential Revisions

1. Include the MRI

A: We have included a magnetic resonance images in the manuscript.

2. Inclusion of a figure with the timeline of clinical events and relevant laboratory findings

A: We have included a figure with the timeline of main events. A Table with relevant laboratory findings had already been included.

3. "Interestingly and contrasting with such a severe presentation in our patient, his wife was asymptomatic throughout her acute stage of the infection but also required HAART after one year of follow-up, alongside her husband" - There is nothing particular in this fact. Between people infected by the same virus, acute and chronic clinical manifestation are in the majority, independent and often different.

A: We have excluded all information regarding the patient’s wife.