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Dr Fregni
Editor-in-Chief
World Journal of Neurology

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Dear Dr Fregni,

You will find attached the revised version of an Editorial entitled: "HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis: clinical presentation and pathophysiology" for *World Journal of Neurology*. I have been invited to write this manuscript by Mr Ma.

We would like to thank the Reviewers for their useful comments and hope that the manuscript is now suitable for publication in the *World Journal of Neurology*. Changes are indicated in red in the revised version.

The answers to the Reviewers comments are presented below.

Reviewer 1.

1) "The clinical section is poor developed, what is the age at the onset?, survival? "

The clinical section has been developed with now six paragraphs.

We added the following paragraph concerning the history of the disease.
"Symptoms usually begin around age 30. Most patients have insidious course progressing over months to years. Median time from onset to use of a cane is 6 years, a walker at 13 years, and a wheelchair at 21 years. About 10-20% progress to severe gait impairment over 1-3 months. More rapid progression tend to occur in patients older than 50 with a high viral load, or after blood transfusion, or organ transplantation. However, onset and course are highly variable. Disease usually begins with asymmetric leg weakness and stiffness. Progressively, other leg becomes involved over months or years. Spasticity then become more pronounced. Impairment of ambulation soon appears."

2) "Delete this sentece: For some authors, HTLV-1 can infect microglial cells [12], while for others microglial cells are not infected by HTLV-1 [13], because you mentioned that is controversial, just adjust your references."

The sentence has been deleted.

3) "I dind founf any proposal from the author to improve the animal models or humans studies to the next step of research."

Actually, the last paragraph of the initial version was dedicated to the development of new methods aiming to improve animal models of TSP/HAM. Here is this paragraph.

"New ways of inoculating HTLV-1 should be investigated. HTLV-1-infected MT-2 cells have been used so far; however, most of the work has been done in newborn WKAH rats injected i.p. with these cells and TSP/HAM appears after at least one year in this model. The BBB might prevent HTLV-1-infected MT-2 to reach the CNS. It has been shown that faster and more reproducible results were obtained in adult mice with a direct intra-cerebral injection of these cells [20], suggesting that BBB might be a critical factor. One way to circumvent the BBB would be to cause a breach of it for example by using an i.p. administration of mannitol before injecting HTLV-1-infected MT-2 [31]. Inoculating cells in the cisterna magna, an area close to the spinal cord, following i.p. injection of mannitol would be less traumatic and more simple than directly into the brain or lateral ventricle [32]. Alternatively, intravenous injection of whole blood of patients with prior administration of mannitol, could be realized [33]. Moreover, it has been shown *in vitro* that BBB is abnormal in HTLV-1 related injury, and the previously described models could mimic these features [2].
In conclusion, more studies are necessary to define the pathophysiology of TSP/HAM. Better animal models can pave the way for novel therapeutic approaches."

Reviewer 2.

1) "However, the title of the manuscript "Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy: clinical presentation and Pathophysiology" by Louboutin does not correlate with the contents: 1.Little, if anything, is discussed about "clinical presentation" differential diagnosis, course of the disease, clinical variations, etc."

The clinical section has been developed with now six paragraphs, and includes differential diagnosis, clinical variations, course of the disease, etc.

2) "Little, besides experimental models in lab animals is discussed about determinants, differences of pathophysiology between TSP and ATL, theoretical discussion of multiple pathology of viral origin, etc."

Determinants, differences of pathophysiology between HAM/TSP and ATL, and discussion of other viral myelopathies are now described in three paragraphs.

We believe that this manuscript can be of interest to the readership of *World Journal of Neurology*.

Thank you very much.

Best regards.

Jean-Pierre Louboutin, MD, PhD

3/25/15

PS. There is no conflict of interest concerning this manuscript.