Author's response to reviews

Title: Cerebral toxoplasmosis in Acquired Immunodeficiency Syndrome (AIDS) patients also provides unifying pathophysiologic hypotheses for Holmes tremor.

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Cerebral toxoplasmosis in Acquired Immunodeficiency Syndrome (AIDS) patients also provides unifying pathophysiologic hypotheses for Holmes tremor.

Response to reviewers’ comments

Reviewer 1

- **Major Compulsory Revisions:**

  In relation with the case-report titled: “Cerebral toxoplasmosis in Acquired Immunodeficiency Syndrome (AIDS) patients also provides unifying pathophysiologic hypotheses for Holmes tremor” I think that it is an interesting, and well documented case, but following the instructions of the editors, case reports should make a contribution to medical knowledge. I appreciate the interest, but I do not consider it exceptional for publication at this moment. It could be more relevant if this case indicates more clearly the role that can really play the thalamo-cortical and/or the dentato-rubro-olivary pathways in the pathophysiology of Holmes tremor.

  **Response** - Concerning the role of the cerebello-thalamo-cortical/dento-rubro-olivary pathways in the pathophysiology of Holmes tremor, in our patient, the postero-lateral thalamus was involved and edema extended downwards to the brain stem; we hypothesized that cerebello-thalamo-cortical and/or dento-rubro-olivary tracts were damaged. In addition to mentioning this point in the discussion (please read below), we have now included a table summarizing literature reports on Holmes tremor and Toxplasmosis/AIDS along with our observation, with emphasis on radio-clinical correlation so as to bring out more clearly, the role of cerebello-thalamo-cortical/dento-rubro-olivary pathways in Holmes tremor.

  “Because in our patients, the postero-lateral thalamus was involved, the cortico-thalamic tracts may have therefore been damaged. In all cases of Holmes tremor in AIDS patients with cerebral toxoplastic abscess reported in the literature, various anatomical locations of brain abscesses were associated with Holmes tremor (Table 1). The unifying feature of all these observations is the involvement of either the cerebello-thalamo-cortical and/or the dentato-rubro-olivary pathways”

- **Minor revision**

  I advise authors to update the bibliography related to Holmes tremor. The Clinical and neuroimaging studies in Holmes tremor. Wedges A et al. Acta Neurol Scand 2010 Jan 15

  **Response** - fixed.

Reviewer 2:

- **Major Compulsory revisions:**

  The authors report nicely on a case of Holmes tremor in an AIDS patient with toxoplastic abscess involving thalamus and midbrain. The two additional videos show the symptoms and its disappearance. However, following the journals requirements for publishing.
1. Unreported or unusual side effects or adverse interactions involving medications. The link between the intervention and the reaction should be based on as many as possible of the following:

- Time relation between intervention and reaction
- Dose response relation
- Withdrawal of treatment and re-challenge
- Supportive evidence from previous reports
- Biological rationale

2. Unexpected or unusual presentations of a disease

3. New associations or variations in disease processes

4. Presentations, diagnoses and/or management of new and emerging diseases

5. An unexpected association between diseases or symptoms

6. An unexpected event in the course of observing or treating a patient

7. Findings that shed new light on the possible pathogenesis of a disease or an adverse effect; it seems to the reviewer that the authors missed to outline their unique new finding as they cite at least a few earlier reports that describe Holmes tremor in AIDS patients with toxoplasmic abscess involving thalamus and midbrain before.

Unfortunately the authors do not point out what part of their observations meets the above mentioned criteria.

Response - In order to comply with the journal requirements, we have now emphasized on the unusual presentation of this case and how it could potentially contribute to the understanding of the current pathophysiology (Please read below).

"Because of the location of (1) the lesion in the postero-lateral thalamus, the extension of surrounding edema to the brain stem and (2) the short delay from initial neurological deficit to tremor onset, this case may strengthen the currently suggested pathophysiological mechanisms of the disease”

(1) The location of the abscess in the thalamus and the internal capsule with extensive edema involving the midbrain and its potential in damaging the cerebello-thalamo-cortical/dento-rubro-olivary pathways and the nigro-striatal pathway. We purposefully did a Medline search on Holmes tremor in AIDS patients with cerebral toxoplasmosis abscess to support the findings in our patient. We have shown that in this specific etiology, Holmes tremor was always associated with possible lesions on the cerebello-thalamo-cortical/dento-rubro-olivary pathway and not necessary the nigro-striatal pathway. We have now mentioned the DaTSCAN study by Strecker K and al in a patient with cerebral toxoplasmosis. Our case along with other cases in the literature is in line with Wedges A et al’s findings and conclusions in a recent publication on the role of the nigrostriatal system in Holmes tremor (please read below). By updating the bibliography with Wedges’ paper and bringing forward the SPECT approach in AIDS
patients with cerebral toxoplasmosis, we believe we have improved the originality and the interest of our paper.

The nigrostriatal system was not involved in all reported cases of toxoplasmic-related Holmes tremor. There is one report of DaTSCAN SPECT study in AIDS and Holmes tremor related to a toxoplasmic abscess (6). The author showed that there was a left-sided reduction in dopamine transporter 4 months following a treatment of cerebral toxoplasmosis. Recently, in a retrospective DaTSCAN SPECT study of six patients with Holmes tremor, there was no remarkable visual difference in presynaptic dopaminergic nigrostriatal system involvement. The authors concluded that nigrostriatal pathway damage may not be crucial for the development of Holmes tremor.”

(2) Except for one case where this delay is not mentioned, our case describes the shortest delay from initial neurological deficit to tremor. This very short delay and the dramatic improvement of the tremor could potentially support the theory of the secondary neuronal degeneration in Holmes tremor (please read below).

“In our patient, the delay from initial neurological deficit to the onset of tremor was only eighteen days. In previous reports, this delay (when available) ranged from 1 month to 5 months (4-7). The role of a secondary degeneration in the mechanisms of tremor has been advocated as it usually arises as a delayed manifestation of the initial lesion (3). In our observation and in that of Mattos (4), tremor occurred within one month of initial neurological deficit. Unlike other cases of Holmes tremor including those related to toxoplasmic abscess, in these two cases, there was a dramatic improvement of the tremor while on antitoxoplasmic/steroid treatment.”

- Minor revision

The label of figure 1 is wrong: 'figure 2'

Response - Fixed

In the discussion the possibility of spontaneous relief in cases of holmes tremor should be mentioned as well as the possible effect of the antitoxoplasmic and prednisolone therapy on the tremor.

Response - We have now mentioned the possible role of antitoxoplasmic drug and steroids in relieving the tremor as well as that of spontaneous relief of Holmes tremor and point out its usual occurrence within one year of onset (Please read below).

“Unlike other cases of Holmes tremor including those related to toxoplasmic abscess, in these two cases, there was a dramatic improvement of the tremor while on antitoxoplasmic/steroid treatment. It is likely that in our case, neuronal integrity was restored before degeneration was initiated and very unlikely that the improvement could have occurred spontaneously as reported cases of spontaneous relief occurred within one year of tremor onset.”