Author's response to reviews

Title: Progressive dementia associated to ataxia and obesity in patients with Tropheryma whippelii encephalitis

Authors:

Florence Fenollar (florence.fenollar@univmed.fr)
François Nicoli (francois.nicoli@ap-hm.fr)
Claire Paquet (claire.paquet@lrp.aphp.fr)
Hubert Lepidi (hubert.lepidi@univmed.fr)
Patrick Cozzone (patrick.cozzone@univmed.fr)
Jean-Christophe Antoine (j.c.antoine@chu-st-etienne.fr)
Jean Pouget (jean.pouget@ap-hm.fr)
Didier Raoult (didier.raoult@gmail.com)

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Author's response to reviews: see over
To the Editor in Chief
BMC Infectious Diseases

Dear editor,

Please find our answers (in bold) to the editorial request and the reviewer for the manuscript of “Obesity and progressive dementia associated with *Tropheryma whippelii*” from Fenollar et al. for BMC Infectious Diseases. The modifications are marked in yellow in the text.

**Editor report:**

Thank you for your patience during the re-review process. Unfortunately, one of the original reviewers was unable to provide advice on your revised manuscript and as a result we approached a member of our Editorial Board to assess your revised manuscript. Your manuscript has now been re-reviewed.
Editorial requests:

- We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service.

   As suggested, we have used a professional copyediting service.

- Please provide the name of the ethical committee that gave approval for the study:

   The ethical committee that gave approval for the study is a local ethic committee from IFR 48 (Marseille, France). This information is given line 92.

- Please provide all the authors' email addresses on the Title page of the manuscript.

   All the email addresses have been provided on the Title page of the manuscript.

Reviewer's report:

I have a number of comments regarding this manuscript, as follows:

1. In the title and in the body of the manuscript, the authors make the point of the presence of obesity in their patients. I have a concern with this being considered a major factor. They only describe the presence of obesity in 2 of their 5 patients (only 2 of the total of 20 patients). In fact, in one of the patients, he only developed weight gain when he relapsed, not with the original infection. Given these low numbers, how can they consider this to be so important?

   In this manuscript, we want to report our own experience as well as to review the literature. For us, two of the 5 patients that have been seen and followed by one of us (DR) in consultation have developed weight gain in association with their T. whipplei
infection. For our index patient, at the time of the diagnosis, he was handicapped and obese with an increasing weight of 25 kilograms at the time of the diagnosis. He could not almost any more moved and was in a bed in a hospital room. After only 2 months of antibiotic treatment, he had lost 17 kg. For the other patient, even if it was at the time of the relapse, he developed an obesity in association with his *T. whipplei* infection.

Even if the overall number (2 of the total of 17, after checking of the presence of enough data to get definitive information about weight gain, as suggested by the reviewer in the query 10) seems low, the information of the association of obesity and *T. whipplei* infection is important for us. *T. whipplei* is usually associated to a weigh loss. Finally, we want to attract attention of physicians to think about *T. whipplei* infection in presence of recent obesity and dementia.

2. On line 224 and in Table 2, the dose of trimethoprim-sulfamethoxazole indicated is 320/3200. I need clarification here, as the usual dose of tablets is a 1:5 ratio, not 1:10. A single strength tablet has a 40 mg of trimethoprim and 320 mg of sulfamethoxazole.

The reviewer is right there is a mistake in the indicated dose of trimethoprim-sulfamethoxazole. Sulfamethoxazole and trimethoprim is available in two kinds: in tablets, each containing 400 mg sulfamethoxazole and 80 mg trimethoprim for oral administration and in double strength tablets, each containing 800 mg sulfamethoxazole and 160 mg trimethoprim. We have treated our patients with two double strength tablets three times a day. Thus, the indicated dose of trimethoprim-sulfamethoxazole must be 320-1,600 mg/day 3 times/day. We have performed the corrections throughout the text and the Table 2.
3. Line 250, should be central nervous system.

   **We have performed the corrections.**

4. First paragraph of the discussion indicates that this is a disease of middle age men. However, the age range of the patients was 33-72 years, with 6 of the patients less than or equal to 40 years of age, and 40% of the patients were women (8 of 20). Therefore, I don’t understand their characterization. In that paragraph, they also indicate their patients would certainly have died without treatment - how do they state this with certainty when there have been only 3 patients reported in the literature who have died?

   **In the first paragraph of the discussion, we have mainly focused on our personal experience and the 5 patients that have been diagnosed in our center. They were middle age men and their condition was very poor and worsening at the time of the diagnosis. It is why we considered that without antibiotic treatment, they would certainly died. Besides, when we have started the antibiotics, an improvement has been very quickly observed. For example, for our index patient, the medical staff as well as the patient and his family were extremely astonished of such improvement in a short time.**

   As suggested, we have moderated our remarks in our first paragraph sentences, we say : “We describe a clinical phenomenon of patients with *T. whipplei* who present with isolated brain involvement and respond dramatically to antibiotic treatment. Their condition was poor and worsening at the time of the diagnosis. Their outcome could have been fatal if they had not been treated.” instead of “We describe a clinical entity of middle age men who present with isolated brain involvement with *T. whipplei* and respond dramatically to antibiotic treatment. If our patients had not been treated, they...
would certainly have died. Their condition was poor and worsening at the time of the diagnosis.”

5. Lines 353 and 354, I don't like the terms "spectacular" effect.

   As suggested, we have deleted “spectacular” effect and used “quick effect”.

6. In the final paragraph of the discussion, the authors suggest that patients with unexplained progressive dementia, generally associated with ataxia or recent obesity, should get a trial of antibiotic therapy. I find this to be a very surprising conclusion - that is, to suggest that a patient be put on an empiric trial of 15-18 months of therapy with no diagnosis. Are they serious about this recommendation?

   We didn’t want to suggest to put a patient on an empiric trial of 15-18 months of therapy with no diagnosis. We only wanted to suggest to consider to test if an empiric antibiotic treatment will be efficient for these patients as their condition was poor and antibiotics treatment quickly efficient. Thus, if the empiric antibiotic treatment is inefficient, it will be quickly stopped. However, to not lead to misinterpretation, we have deleted this suggestion of our final paragraph. In conclusion, we only underline that “patients respond dramatically to antibiotics”.

7. Page 17, which lists the legends. Table 1 is not a summary of patients with T. whipplei chronic encephalitis - that is Table 2. The legend for Table 2 is really the one for Table 3. I am not sure of the purpose of Figure 1 - that is, to show histopathology of someone without T. whipplei encephalitis.
We have corrected the list of the legends. As suggested, we have also deleted the Figure 1.

8. Table 1. I do not understand how 3 patients with positive PAS staining can be excluded as having the diagnosis when PCR testing was not performed. Are the authors also saying that a negative PCR absolutely excludes the diagnosis of *T. whipplei* encephalitis? Did these patients all have encephalitis?

In this Table, we would like mainly to underline that: (1) the PAS staining of brain biopsies is not specific of *T. whipplei* as the analyses of the same brain samples using the immunohistochemistry performed with polyclonal rabbit antibodies specifically directed against *T. whipplei* were negative (2) *T. whipplei* infection can be observed even if PAS staining and specific immunohistochemistry are negative.

For the patients with positive PAS staining whom have been excluded as having the diagnosis when PCR testing was not available: the positive PAS staining is not linked to the presence of *T. whipplei* as the immunohistochemistry performed with polyclonal rabbit antibodies specifically directed against *T. whipplei* was negative. However, the reviewer is right we cannot definitely excluded the patients as having the diagnosis when PCR testing was not available. Thus, according to this remark, we have modified our Table, creating a new group of patients for whom the diagnosis of *T. whipplei* encephalitis was not available in lack of PCR. Besides, we have also added why PCR assays were not available for these patients. Indeed, no fresh specimens have been sampled for these patients and the quality of the extracted DNA from the paraffin-embedded specimens was poor, not allowing a conclusion for the molecular assays.
If the quality of the DNA extracts from brain biopsies has been confirmed and the sampling performed in patients without antibiotic treatment or after a therapeutic window, a negative PCR excludes the diagnosis of \textit{T. whipplei} encephalitis. Finally, all the patients included in Table 1 have encephalitis. We have added this information in the new legend.

9. Table 2, patient #7 was in 2 references - are they the same patient in two different publications?

Yes, this is the same patient in two different publications. We have clarified the legend of Table 2 adding that we present the data of 20 patients and that in brackets we have the respective references of the patients.

10. Table 3, the heading of the last column should be Patients with certain or possible \textit{T. whipplei} encephalitis. In that column with data taken from Table 2, 12/20 patients were male. For the cases reported from the literature, was there enough information to get definitive information as to whether all of the patients had arthritis, arthralgias, chronic diarrhea, and weight gain. In other words, were these reported as being present or absent in ALL cases?

We have corrected the heading of the last column and the rate of male patients. As suggested, we have carefully checked for the cases reported from the literature of the presence of enough information to get definitive information about the absence or the presence of arthritis, arthralgias, chronic diarrhea, or variation of weight. For arthralgia, arthritis and chronic diarrhea, definitive information is clearly given for 13 out of 15 patients. For variation of weight, definitive information is clearly given for 12
out of 15 patients. Thus, we have corrected all the data according to the definitive information in Table 3 as well as throughout manuscript.

11. Table 4 needs a little more explanation for me. In the second column on Whipple's disease with neurologic manifestations, I would assume that many of these patients had encephalitis, especially since 72% had cognitive impairment. This is being compared to their 20 patients with Whipple's encephalitis, so I am not that surprised there were some statistical differences, given the likely expectation that many of the 74 patients with neurologic Whipple's had other neurologic conditions and not encephalitis. Were some of their 20 patients also part of the 74 previously reported in the literature?

In Table 4, we only compare the neurologic manifestations of patients with Whipple’s disease (i.e. patients with an histological digestive involvement characterized by a positive PAS staining) with associated neurologic manifestations to patients with *T. whipplei* encephalitis (without histological digestive involvement). None of the 20 patients with *T. whipplei* encephalitis also part of the 74 previously reported in the literature with Whipple’s disease with associated neurologic manifestations.

As suggested by the reviewer, we have clarified the legend of Table 4: “Clinical features* of 74 patients with Whipple’s disease (i.e. patients with an histological digestive involvement characterized by a positive PAS staining) with neurologic manifestations and those with certain (13) and possible (7) *T. whipplei* chronic encephalitis without digestive lesions.”

12. Spelling issues throughout the text: trimethoprim-sulfamethoxazole and myorhythmia.
We have corrected trimethoprim-sulfamethoxazole and myorhythmia throughout the text.

- Level of Interest: An article of interest in its field.

- Quality of written English: Acceptable, but will need some editorial review.

We have used a professional copyediting service.

- Statistical review: Not needed.

Sincerely yours,

Pr Didier RAOULT