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OPEN PEER REVIEW

Serum Evaluation of Human T-lymphotropic Virus Type 1 and 2 (HTLV-I/II) and Human Immunodeficiency Virus (HIV) in Patients with Multiple Sclerosis (MS)

Zahra Golmohammadi, Reza Boostani, Morteza Saeidi, Ehsan Aryan, Aida Gholoobi, Mojtaba Meshkat, Amin Hooshyar Chechaklou, Mahdieh Khoshakhlagh, Samaneh Abolbashari, Zahra Meshkat

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This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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Contents

1 **Original submission** Abdorreza Moghadasi, Seyed-Amirabbas Ahadiat, Referee 1, Associate Editor, Edi... 2

2 **Revision 1** Seyed-Amirabbas Ahadiat, Associate Editor, Editor-in-Chief 4

Authors' reply to reviewers 5

Reviewer and editor comments 11

3 **Revision 2** Seyed-Amirabbas Ahadiat, Referee 1, Associate Editor, Editor-in-Chief 12

Authors' reply to reviewers 13

Reviewer and editor comments 14

1 Original submission

5 comments · 4 Apr 2023 – 29 May 2023

Abdorreza Moghadasi Reviewer

REJECT 4 Apr 2023

This study doesn't add anything to the literature. Please describe the message that the authors want to convey by writing this article.

Seyed-Amirabbas Ahadiat Reviewer

MINOR REVISION 28 May 2023

dear author

The relationship between HIV and MS has been investigated for years, but a clear connection between the two has still not been determined, so your study can be useful.

If you can briefly discuss the pathophysiological relationship between these two diseases or recent developments in the relationship between HIV and MS in the discussion section of the article, your study will be much stronger, so I refer you to the following two studies that you can use as references:

1-Gudowska-Sawczuk M, Mroczko B. Free light chains as a novel diagnostic biomarker of immune system abnormalities in multiple sclerosis and HIV infection. BioMed Research International. 2019 Dec 9;2019.
2-Stefanou MI, Krumbholz M, Ziemann U, Kowarik MC. Human immunodeficiency virus and multiple sclerosis: a review of the literature. Neurological research and practice. 2019 Dec;1:1-7.

Of course, there are several language issues; having the article edited by a native English speaker will make it more appealing to readers.

Also, in the methods section, explain what method was used to diagnose MS in the patients. Was a guideline used?

Did the people you used in the control group not have a family history of neurological disease or MS? Why were people in the control group hospitalized?

Referee 1 Reviewer

MAJOR REVISION 29 May 2023

The study design and methods are clearly described, and the results are presented in a concise manner. However, there are a few aspects that could be improved to enhance the quality and impact of the review.

Introduction:
The introduction provides a general overview of MS, its prevalence, and the involvement of genetic and environmental factors. To strengthen the introduction, it would be beneficial to include more specific information on the potential role of infectious microorganisms, such as retroviruses, in the pathogenesis of MS. This could involve citing key studies or summarizing the existing literature on this topic.

Methodology:
The description of the study design and population is clear. However, additional details regarding the selection criteria for MS patients and controls would be helpful. Including information on how MS diagnosis was confirmed and how controls were matched to the case group would improve the study's methodological rigor.

Data Analysis:
The statistical analysis section provides a clear description of the tests used, such as the Kolmogorov-Smirnov test, Student's t-test, chi-square test, and Fisher's exact test. However, it would be beneficial to include information on how missing data, if any, were handled and whether any adjustments were made for potential confounding variables.

Discussion:
The discussion section effectively compares the study findings with previous research. However, it would be valuable to provide a more in-depth analysis and interpretation of the results. Specifically, discussing the potential implications of the absence of HTLV-I/II and HIV antibodies in MS patients and its relevance to the etiology and pathogenesis of MS would strengthen the discussion section.

Limitations and Future Directions:
The review would benefit from a section addressing the limitations of the study. This could include aspects such as the small sample size, the specific ELISA kits used, and potential confounding variables that were not accounted for. Additionally, suggesting avenues for future research, such as investigating other infectious agents or using more sensitive detection methods, would further contribute to the discussion.

Conclusion:
The conclusion provides a concise summary of the study findings. However, it would be valuable to emphasize the implications of the findings and their relevance to the current understanding of the association between HTLV-I/II, HIV, and MS. Additionally, highlighting the need for further research to explore the potential role of other infectious agents in MS would enhance the conclusion.

Formatting and Language:
The article adheres to a clear structure and uses appropriate language. However, proofreading for grammar and typographical errors would further improve the quality of the writing.

Associate Editor

MAJOR REVISION 29 May 2023

Dear EIC,
This systematic review contributes to the existing knowledge on the relationship between HTLV-I/II, HIV, and MS. To enhance the impact of the review, it is recommended to provide more specific information in the introduction, include additional methodological details, offer a more in-depth analysis and interpretation of the results, address the study's limitations, and emphasize the implications of the findings in the conclusion.

Editor-in-Chief

MAJOR REVISION 29 May 2023

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for considering our manuscript for publication in the Archives of Neuroscience. We have read the valuable comments of the reviewers and have made changes in the manuscript where necessary.

Below is our reply to the reviewers' comments:

Reviewer1:

This study doesn't add anything to literature. please describe the message that authors want to tell by writing this article.

R: The aim of our investigation was to explore the presence of HTLV-I/II and HIV antibodies in the serum of individuals residing in northeastern Iran who are diagnosed with MS. This investigation has not been done before in the mentioned population. The message is that MS is not related to the presence of antibodies against HIV and HTLV- I/II in this area.

Reviewer2:

dear author

Examining the relationship between HIV and MS has been being tested for years, but still, a clear connection between the two has not been determined, so your study can be useful study.

-If you can briefly discuss the pathophysiological relationship between these two diseases or recent developments in the relationship between HIV and MS in the discussion section of the article, your study will be much stronger, so I refer you to the following two studies that you can use as a reference

1-Gudowska-Sawczuk M, Mroczko B. Free light chains as a novel diagnostic biomarker of immune system abnormalities in multiple sclerosis and HIV infection. BioMed Research International. 2019 Dec 9;2019.

2-Stefanou MI, Krumbholz M, Ziemann U, Kowarik MC. Human immunodeficiency virus and multiple sclerosis: a review of the literature. Neurological research and practice. 2019 Dec; 1:1-7.

R: We added the findings of the mentioned study to the manuscript:

The relationship between HIV and MS has been an area of interest in medical research. While both are distinct diseases with different underlying mechanisms, there have been studies exploring potential associations and interactions between them. Both HIV and MS involve the immune system, through different ways. HIV is primarily known for its ability to suppress the immune system, specifically targeting CD4+ T cells (39). Consequently, lower activation of immune system can lead to lower manifestation of MS as an autoimmune disease. HIV infection can lead to various neurological complications, including cognitive impairment, peripheral neuropathy, and opportunistic infections affecting the central nervous system. These complications may mimic MS symptoms or be misdiagnosed as MS, highlighting the importance of accurate diagnosis and differentiation between the two conditions. Furthermore, several studies have indicated the presence of shared risk factors between HIV and MS, including genetic susceptibility and environmental factors. However, the absence of HIV antibodies in MS patients suggests that active HIV infection is not a major factor contributing to the development of MS (40). The evidence supporting a direct causal link between the two diseases remains limited and requires further investigation. This finding supports the understanding that MS is primarily an autoimmune disease rather than a consequence of HIV infection.

Of course, there are a series of editing problems that will be more attractive for readers if you edit natively

R: The manuscript was edited grammatically.

-Also, in the methods section, explain what the method of diagnosing MS patients was? Was the guideline used?

R: All patients who were diagnosed with MS and provided written consent to participate in the study were included during the enrollment period at the neurology clinic. The diagnosis of MS typically involves a combination of clinical evaluation, medical history assessment, neurological examination such as MRI, and various diagnostic tests. The process aims to rule out other conditions with similar symptoms and establish the presence of characteristic features suggestive of MS. The diagnosis of MS was based on McDonald criteria, which incorporate clinical, imaging, and laboratory findings to enhance the accuracy and efficiency.

-The people you used in the control group did not have a family history of neurological disease or MS? Why were people in the control group hospitalized?

R: The individuals in the control group did not have a family history of neurological disease or MS. Their serum samples were selected as controls due to their residency in the same city, making it convenient to obtain samples. Each participant in the control group was admitted to a different ward for reasons unrelated to neurology, ensuring a diverse range of medical conditions among the control group.

Reviewer 3:

The study design and methods are clearly described, and the results are presented in a concise manner. However, there are a few aspects that could be improved to enhance the quality and impact of the review.

Introduction:

The introduction provides a general overview of MS, its prevalence, and the involvement of genetic and environmental factors. To strengthen the introduction, it would be beneficial to include more specific information on the potential role of infectious microorganisms, such as retroviruses, in the pathogenesis of MS. This could involve citing key studies or summarizing the existing literature on this topic.

R: One specific retrovirus that has been studied in relation to MS is the Human Endogenous Retrovirus (HERV). HERVs are remnants of ancient retroviral infections that have become a part of the human genome. Some studies have reported increased expression of HERV-related elements in MS patients, particularly in active MS lesions. It has been hypothesized that the expression of HERV elements could lead to inflammation and immune dysregulation, contributing to MS pathogenesis. However, further research is needed to fully understand the significance and mechanisms of HERV involvement in MS. Besides retroviruses, other infectious agents have been investigated as potential triggers for MS or contributors to disease progression. For example, Epstein-Barr virus (EBV), a member of the herpesvirus family, has been extensively studied in relation to MS. Epidemiological studies have shown an association between prior EBV infection and an increased risk of developing MS.

Methodology:

The description of the study design and population is clear. However, additional details regarding the selection criteria for MS patients and controls would be helpful. Including information on how MS diagnosis was confirmed and how controls were matched to the case group would improve the study's methodological rigor.

R: All patients who were diagnosed with MS and provided written consent to participate in the study were included during the enrollment period at the neurology clinic. The diagnosis of MS typically involves a combination of clinical evaluation, medical history assessment, neurological examination such as MRI, and various diagnostic tests. The process aims to rule out other conditions with similar symptoms and establish the presence of characteristic features suggestive of MS. The diagnosis of MS was based on McDonald criteria, which incorporate clinical, imaging, and laboratory findings to enhance the accuracy and efficiency. The results were compared to the control group, which consisted of 41 serum samples obtained from patients admitted to other wards of Ghaem hospital. These control group patients did not exhibit any symptoms of MS and were matched with the MS patients in terms of sex and age.

Data Analysis:

The statistical analysis section provides a clear description of the tests used, such as the Kolmogorov-Smirnov test, Student's t-test, chi-square test, and Fisher's exact test. However, it would be beneficial to include information on how missing data, if any, were handled and whether any adjustments were made for potential confounding variables.

R: We did not have any missing data and no adjustment was necessary.

Discussion:

The discussion section effectively compares the study findings with previous research. However, it would be valuable to provide a more in-depth analysis and interpretation of the results. Specifically, discussing the potential implications of the absence of HTLV-I/II and HIV antibodies in MS patients and its relevance to the etiology and pathogenesis of MS would strengthen the discussion section.

R: The discussion was revised as follows:

However, the absence of HIV antibodies in MS patients suggests that active HIV infection is not a major factor contributing to the development of MS (40). The evidence supporting a direct causal link between the two diseases remains limited and requires further investigation. This finding supports the understanding that MS is primarily an autoimmune disease rather than a consequence of HIV infection.

Some studies have explored the possible involvement of HTLV-I/II in MS, given their ability to infect T cells and cause immune dysregulation. However, the absence of HTLV-I/II antibodies in MS patients suggests that these retroviruses are unlikely to play a significant role in the pathogenesis of MS. This finding indicates that the mechanisms underlying MS development may differ from those associated with HTLV-I/II-associated diseases.

It's important to note that while the absence of HTLV-I/II and HIV antibodies in MS patients provides valuable insights, it does not completely rule out the possibility of other viral infections or viral triggers playing a role in MS pathogenesis. The complex interplay between genetic, environmental, and immunological factors in MS requires further research to fully understand the disease's underlying mechanisms.

Limitations and Future Directions:

The review would benefit from a section addressing the limitations of the study. This could include aspects such as the small sample size, the specific ELISA kits used, and potential confounding variables that were not accounted for. Additionally, suggesting avenues for future research, such as investigating other infectious agents or using more sensitive detection methods, would further contribute to the discussion.

R: Many studies exploring the association between MS and infectious agents like HTLV or HIV are often observation, such as case-control studies or retrospective analyses. While these studies can provide valuable insights, they have inherent limitations, including recall bias, selection bias, and the inability to establish causality. The other one is small sample sizes, which can limit the statistical power to detect subtle associations or differences. Additionally, sample selection bias may arise due to the recruitment of patients from specific populations, such as specialized clinics or specific geographic regions, which may not be representative of the broader MS population. Studies exploring the relationship between infectious agents and MS need to carefully account for

confounding factors. Factors such as genetic susceptibility, environmental exposures, and other coexisting infections may influence the outcomes and complicate the interpretation of study findings. So, Further research with larger sample sizes, rigorous study designs, and comprehensive consideration of confounding factors is necessary to better understand the potential involvement of infectious agents in MS pathogenesis.

Conclusion:

The conclusion provides a concise summary of the study findings. However, it would be valuable to emphasize the implications of the findings and their relevance to the current understanding of the association between HTLV-I/II, HIV, and MS. Additionally, highlighting the need for further research to explore the potential role of other infectious agents in MS would enhance the conclusion.

R: In conclusion, according to the findings, this study could not specify a possible relationship between the presence of HTLV-I/II or HIV antibodies and MS. Further research can provide more clarity on the specific mechanisms by which infectious agents may influence MS development and progression. MS is a heterogeneous disease with various clinical subtypes and disease courses. It is likely that different infectious agents, or combinations thereof, may play a role in different subgroups of MS patients. Exploring the potential involvement of other infectious agents may help in identifying subtypes or specific patient populations that could benefit from targeted interventions. By expanding our knowledge in this area, we can gain a more comprehensive understanding of the complex interactions between infectious agents, genetic factors, and the immune system in MS, ultimately leading to improved diagnosis, treatment, and preventive strategies.

2 Revision 1

3 comments · 7 Aug 2023 – 8 Aug 2023

Seyed-Amirabbas Ahadiat Reviewer

MINOR REVISION 7 Aug 2023

Dear author

Can you clarify the reason for not ensuring equalization between the treatment group and the control group?

Can you explain the reasoning behind selecting the control group from hospitalized individuals?

To make a proper comparison, it is important to include a control group that is completely healthy and has no history of the disease. This group must undergo the necessary tests for HTLV and HIV infections before the study.

Associate Editor

MINOR REVISION 8 Aug 2023

Dear EIC,
Some revisions have been made, but further revision is still needed.

Editor-in-Chief

MINOR REVISION 8 Aug 2023

Dear Author,
Although some changes have been made, some revision is still needed. You have another chance to revise this manuscript.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for considering for publication in the Archives of Neuroscience. *We have read the valuable comments of the reviewers and have made changes in the manuscript where necessary.*

Below is our reply to the reviewers' comments:

Q1: Can you clarify the reason for not ensuring equalization between the treatment group and the control group

R: We performed frequency matching in the present study based on ensuring that the distribution of certain variables is the same among cases and controls.

Q2: Can you explain the reasoning behind selecting the control group from hospitalized individuals?

R: We chose the control group due to the presence of available patients, their residency in the same city, and the acquisition of individual consent.

3 Revision 2

4 comments · 27 Aug 2023 – 1 Sep 2023

Seyed-Amirabbas Ahadiat Reviewer — ACCEPT — 27 Aug 2023

Thank you for your revision.

Referee 1 Reviewer — ACCEPT — 1 Sep 2023

Dear EIC,
The great effort in improving the manuscript is highly appreciated.
The authors have addressed all comments.

Associate Editor — ACCEPT — 1 Sep 2023

Dear EIC,
The manuscript can be accepted now.

Editor-in-Chief — ACCEPT — 1 Sep 2023

Dear Author,
Thank you for correcting the pitfalls and answering all questions. The manuscript is acceptable now.