Dear Dr Keely Cheslack-Postava: comment 6

Very few subjects overall (N=3) were positive, therefore, it is difficult to draw conclusions from this study and it was clearly underpowered. The authors should discuss what they hypothesize to be the relevant time window of exposure to the virus with regard to disease status, and how this relates to what was measured in this cross-sectional study. Perhaps a different time point in life or disease history is more relevant for risk of SCZ/BD?

We thought that if during the disease we could find higher viral load in the patients in comparison with the healthy controls, we could say that may be there is relationship between active infection (recent infection or reactivation) and these diseases. But we could not able to detect enough positive results to compare and analysis.

We added:

we designed the study to use a sensitive method for detection of HHV-6 DNA in PBMCs to show the latent infections in both patients and HCs and then continue the study for DNA detection in plasma and comparison the viral load in patients and HCs for finding the active infections and possible relationship with these diseases, but because of low detection rate in PBMCs we ignored to work on plasma.

May I ask you to help me if the article needs some more improvements?

I don’t know how to appreciate your help and valuable comments.

Dear Dr Duncan Sinclair: comments 1a and 1b. Please do not delete reference Nitschce et al., but discuss their findings in the context of the current study.
1) As mentioned by a previous reviewer, the low number of individuals in whom HHV-6A/B-positive PBMCs were detected makes interpretation of any disease association difficult. This does not necessarily mean the study should not be published. However, the issue should be discussed thoroughly. In particular:

a) The number of positive individuals should be provided in the abstract, and the lack of statistical power to identify diagnostic differences mentioned in the discussion

b) The rationale for detection of viral DNA in PBMCs rather than whole blood or plasma should be provided in the manuscript, rather than in responses to the previous reviewer. It should also be described more clearly. Does HHV-6 DNA in PBMCs reflect persistent, low level active infection in tissue, even in the absence of HHV-6 DNA in plasma (this appears to be what is suggested)? If so, references would be helpful, particularly given that the study by Nitsche at colleagues (ref. 24) suggests that HHV-6 DNA measurement in PBMCs is less sensitive than in plasma, especially for HHV-6A since HHV-6A was undetectable in PBMCs but detectable in plasma.

The discussion was completed.

Reference 22 needs to be corrected and should not be link to a pdf document (that I did not manage to open).

I checked the article and honesty I did not have any problem with this article.

May I ask you to help me in this regard and clarify the problem? Otherwise I can change the reference.

May I ask you to help me if the article needs some more improvements? I don’t know how to appreciate your help and valuable comments.

Dear Dr Glenn Konopaske: Major point 3: ANOVA analysis should be undertaken for the 3-group comparison. Minor point 3 and discretionary point 2: what was the specific instrument/diagnostic exam used to assess these psychiatric disorders, which as the authors state was according to DSM-IV criteria?

3) Since there are three groups, independent t-test are inappropriate for the continuous variables. An ANOVA followed by post-hoc comparisons controlling for multiple comparisons (e.g., SNK or Dunnett's) should be done.

Actually we compared all patients (BD and SC patients) with controls. It means we had two groups, one group was patients and the other group was controls and because of that we used t-test and we mentioned under the table.

3) The following sentence in the conclusion is unintelligible and should be re-phrased: "Huge challenges need to find the pathogenesis..."

we changed and corrected the conclusion.

2) Were the diagnoses of schizophrenia and bipolar disorder confirmed by SCID? If not, why not?

The diagnosis was according to the SCID (It was added).
May I ask you to help me if the article needs some more improvements? I don’t know how to appreciate your help and valuable comments.

Dear Dr Zongchang Li: comment 1
Given rare detection rate of HHV-6 virus in the PBMCs (1.5%) , a false negative result may be caused due to the small sample size included in this study. The conclusion was not adequately supported by the data and a larger sample size was suggested.

We improved the discussion.

May I ask you to help me if the article needs some more improvements? I don’t know how to appreciate your help and valuable comments.