Author’s response to reviews

Title: The performance of rapid plasma reagin (RPR) titer in HIV-negative general paresis after neurosyphilis therapy

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Version: 1 Date: 22 Oct 2017

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Dear editor and reviewers: Firstly, thank you for your comments. According to your comments, I want to do some replies. And we have revised the changes in the manuscript by highlighting with red words. Reviewer reports: Tim Read (Reviewer 1): Thanks for asking me to review “The performance of serum rapid plasma reagin (RPR) titer in HIV-negative general paresis after neurosyphilis therapy” which examines RPR titres in patients with general paresis before therapy and in a small subgroup, after therapy. Patients with RPR+ CSF are compared with those who are RPR negative. General paresis is currently rare in high-income countries but may become more common in one or two decades as a result of the current resurgence in syphilis in MSM. This study provides useful information on whether changes in the serum RPR after treatment can be used to monitor response to treatment, or whether the CSF RPR is a better measure. Opportunities to study general paresis are rare because it is not often seen in settings with good resources for research, so this paper is potentially valuable. I have three major concerns which I believe should be addressed before the paper is published: 1. From the information presented I have some doubt that all patients had general paresis. Could some have had alcoholic dementia, or some other form of dementia, affecting their MMSE, combined with reactive syphilis serology? This is especially relevant to those with normal CSF or non-specific changes in their CSF. It would be helpful to readers, and strengthen your case, to know more about the clinical features of the cases: eg proportions with...
neurologic signs (eg pupillary changes, hyperreflexia, speech changes) and proportions with personality or affective changes or delusions/hallucinations. It is inevitable that there may be some uncertainty, as it is a diagnosis of exclusion, but this shouldn't deter you from providing more clinical information. Answer: Many thanks for your suggestions. Your comments are very important. The GP patients were carefully selected according to the following criteria: (1) serologic testing was based on RPR positivity in CSF, or white blood cell (WBC) count of CSF > 5 cells/μL or protein of CSF > 45 mg/dL with TPPA positivity in CSF [French et al., 2009]; (2) patient with deterioration in memory, personality, and habits, and with disorientation; (3) neurologic and/or psychiatric symptomatology with chronic progressive course and phases of partial remission or deterioration; (4) exclusion of alternative diagnoses, such as dementia resulted from any other disease, including Alzheimer’s disease, vascular dementia, frontotemporal dementia, Parkinson’s disease dementia, multiple system atrophy, metabolic disease (Vitamin B12 deficiency and thyroid hormone deficiency) and poisoning disease (alcoholism and carbon monoxide poisoning), et al. And these patients were carefully diagnosed by excluding alternative diagnoses, especially excluding these causes of dementia. These other causes of dementia certainly include alcoholic dementia. Although alcoholism is one cause of dementia, the significant alcohol use is need for the diagnosis of alcoholic dementia. And the significant alcohol use is defined by a minimum average of 35 standard drinks per week for men, and 28 for women, for a period > 5 yr. The period of significant alcohol use must occur within 3 yr of the initial onset of cognitive deficits [Cheon et al., 2008]. Though some patients in our study drink alcohol, the amount of alcohol of these patients can’t reach the criteria mentioned above. Of course, if we could provide more clinical information, which will be indeed a useful supplement to our manuscript, however the main goal of this study is to explore the RPR titers in evaluating the treatment outcome of neurosyphilis, so we do not collect and analyze too much clinical features of these cases in addition to MMSE scores and the results of CSF examinations in process of writing this original manuscript. Therefore we could not provide the data of difference in symptoms or duration of symptoms between these patient groups in revised manuscript. References: French P, Gomberg M, Janier M, Schmidt B, van Voorst Vader P, Young H; IUST. IUSTI: 2008 European Guidelines on the Management of Syphilis. Int J STD AIDS. 2009; 20(5): 300-309. Cheon Y, Park J, Joe KH, Kim DJ. The effect of 12-week open-label memantine treatment on cognitive function improvement in patients with alcohol-related dementia. Int J Neuropsychopharmacol 2008; 11: 971-983. 2. This study has several significant limitations, but these are not listed in the discussion. Please provide a limitations paragraph which mentions: a) any (I find it hard to accept that you can be certain of diagnoses of neurosyphilis when the CSF RPR is negative particularly when the serum RPR is also negative), b) the very large losses to follow-up and c) any other caveats readers should consider alongside your data. Answer: Many thanks for your comments. We have added a limitations paragraph in the revised manuscript. In previous manuscript, there were three patients whose CSF and serum RPR both are negative. These GP patients included in our study are late syphilis. In late syphilis, the serological response of nontreponemal tests is often absent [Brown and Frank, 2003]. These patients also did essential examinations and took the detailed history of disease to exclude other diseases, thus any other diseases clouding the diagnosis of GP, such as dementia resulted from any other disease, including Alzheimer’s disease, vascular dementia, frontotemporal dementia, Parkinson’s disease dementia, multiple system atrophy, metabolic disease (Vitamin B12 deficiency and thyroid hormone deficiency) and poisoning disease (alcoholism and carbon monoxide poisoning), et al., was excluded. Hence, we consider that three patients whose RPR test in CSF and serum both were negative had the confirmed diagnosis of GP.