Author's response to reviews

Title: Chronic cerebrospinal venous insufficiency in Multiple Sclerosis: an highly prevalent age-dependent phenomenon

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Author's response to reviews: see over
To the Editor-
Dr. Robert Zivadinov
BioMed Central

Dear Dr. Robert Zivadinov,

I would like to submit a new revised copy of our manuscript, n 3697861107767469, entitled “Chronic cerebrospinal venous insufficiency in Multiple Sclerosis: an highly prevalent age-dependent phenomenon”.

We hope we have solved all the criticism of our manuscript and now, in this last version, it is acceptable for publication.

We have upload a file were we answer point-to-point to the reviewer comments.

Thank you again for considering this revised manuscript for publication, if there are any other revisions that the editors and/or reviewers would like, we would be happy to address them.

Best regards

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Major Compulsory Revisions:
1. Abstract. Background. It should begin with: „The aim of our research was to investigate....."
   We changed the abstract accordingly

2. Abstract. Such term like “as previously described” should not be found in an abstract. The sentence should be rewritten.
   The sentence was rewritten

3. Abstract. The authors should unequivocally state which correlation (positive or negative) has been found between the patients’ age and presence of CCSVI.
   The positive correlation was indicated elsewhere in the text-

4. Abstract. “flux” is the Italian word. The proper English term is “flow”.
   The word was corrected

5. Abstract. The authors should not use the term “criterion 4” outside the context. Such a term may be used in the main text. On the contrary, an abstract should be an autonomous document, easily understandable with access to the main text.
   The term criterion 4 was changed with the description

6. Abstract. It would suggest to delete the last sentence. It bears no information. Instead, the authors may give more information (within word limit) in the Results section.
   The last sentence was deleted. More information were added in the Results section: B-mode abnormalities of IJV as stenosis, malformed valves, annulus and septa were the more frequently detected anomalies, both in MS patients (80.8%) and controls (47.4%)

7. Abstract. Abstract should be proofread (English is poor).
   The entire paper was read by a native English

8. Background. The authors are citing small venographic studies (ref. 4, 5, 6), but big ones are not cited. Such studies should also be included.
   New references were added.
9. Results. Clinical characteristics of the patients should be presented first ("MS patients belonged...."), then the results of sonography ("A concordance between.....").

The first paragraph of the results section was rewritten: Demographic and clinical data of MS patients and control groups are shown in Table 1. Significant differences in age, EDSS and disease duration are evident in the subgroups. MS patients belonged to 4 clinical subtypes (53 RR, 58 SP, 19 PP and 16 CIS) and were treated in 71% of cases with various therapies (59 with Interferon Beta-1, 30 with natalizumab, 8 with glatiramer acetate, 3 with fingolimod, 1 with azathioprine and 1 with mithoxantrone). Of the remaining 44 untreated patients, 8 were naïve to any disease modifying therapy, while the others had been previously treated with 1 or more different drugs.

10. Results. "flow" instead of "flux"

The word was corrected elsewhere.

11. Results. The authors should explain how the CCSVI presence was related to age (positively or negatively); correlation coefficients, in addition to p values, will be appreciated.

To assess that CCSVI presence was positively related to age we used a Mann-Whitney U test, so we don’t have a correlation coefficient but only the value of the statistic that is z=3.32

12. Results. “sensitivity and specificity” issues. I would agree with the authors, with the table unchanged, still a commentary should be added. In spite of the fact that these terms have been used in the papers by Zamboni and Zivadinov, there have been already much misunderstanding and controversies associated with the use of such a statistics. In general, from statistical and semantic point of view the terms are not appropriate (the diagnosis of MS is not a gold standard test to diagnose CCSVI !). In addition, taking into account high prevalence of CCSVI in MS patients, standard statistics should be used with caution and a Bayesian approach seems more appropriate (just a comment).

We agree with referee about the use of Bayesian approach, that’s why in the third column of table 2 we also reported the odds ratio values for each criterion. We added a sentence in Results section: “Despite the diagnosis of MS is not a gold standard test to diagnose CCSVI, sensitivity, specificity, and relative odds ratio (OR) between HC and patients with MS were calculated, using direct computation from 2x2 tables, in order to obtain results easily comparable to previous studies”.

13. Discussion. Congenital nature of CCSVI. The authors should present alternative explanations of higher prevalence of CCSVI in older patients, as suggested in the previous review. Also, suggested references should be included and commented. It is not appropriate to discuss only the research that is in line with the beliefs of the authors and to ignore those revealing quite the contrary.

We changed the discussion accordingly and added more citations.
14. Discussion. The authors have found that p value for correlation between the age and presence of CCSVI in the controls was 0.635. It is clearly showing that actually no correlation has been found. Consequently, the authors should not claim for such a correlation in the discussion (perhaps, a correlation coefficient should be given, but such thing as “power=30%”, without statistic method used, is highly confusing. In statistical section it is not reported the statistical method for power calculation because the power calculation is a standard procedure to be applied before performing any statistical test. A power of 30%, as in our case, means that there is a 70% probability that we make an error if we reject the alternative-hypothesis that there isn’t a correlation between CCSVI and age also in HC group.

Moreover, if CCSVI were simply caused by MS (irrespective of the mechanism responsible), one should expect a positive correlation between duration of MS and CCSVI prevalence, which has not been found by the authors.

Regarding the expected positive correlation between duration of MS and CCSVI prevalence, which was not found in our patients, this would be true if we hypothesized a cause effect of MS on CCSVI, but as we write in the Discussion (An interesting hypothesis was raised recently in a paper suggesting that a neurological process could play a role in CCSVI progression, through vasoactive substances (such as endothelin-1) or proinflammatory agents that could act on previously susceptible segments of blood vessels (i.e. malformed vein valves) [45]. This hypothesis would explain the higher prevalence of CCSVI in MS patients and its relation to patients ageing.) we believe that MS might accelerate a progressive ageing of neck veins already predisposed or damaged by themselves.

15. Discussion. The part “In native vessels…durability” should be deleted. It deals with pathology and physiology of arteries and heart, and should not be extrapolated to the veins. Venous physiology and biophysics is very different from that seen in the arteries. We agree that veins and arteries are different entities but they share common features and we used as reference also other papers underlying such parallelism [45].

16. Reference 37. It deals with heart valve pathology. The vein and the heart are two very different things, and the same applies to heart valves and venous valves. We added in the references many studies on venous valves pathology.

17. English has been improved, but there are still parts of the text written in poor English. English language was proofread by a native English.