Author's response to reviews

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

Authors:

Roberta Lanzillo (roberta.lanzillo@unina.it)
Marcello Mancini (marcello.mancini58@gmail.com)
Raffaele Liuzzi (raffaele.liuzzi@cnr.it)
Orlando Di Donato (orlandodd@hotmail.com)
Elena Salvatore (elena.salvatore@unina.it)
Valentina Maglio (valentina.maglio@gmail.com)
Giovanni Vacca (giovagy@libero.it)
luca Amato (amatocir@tiscali.it)
Gennaro D'Anna (gennaro.danna@gmail.com)
Arturo Brunetti (arturo.brunetti@unina.it)
Vincenzo Brescia Morra (bresciamorra@unina.it)

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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 revised copy of our manuscript, n 3697861107767469, now entitled “Chronic cerebrospinal venous insufficiency in Multiple Sclerosis: an highly prevalent age-dependent phenomenon”.

We have found the comments of the two reviewers very useful to improve the manuscript. Therefore, we have accepted and incorporated all them in the manuscript.

We have uploaded 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

Marcello Mancini, MD
Research Director
Institute of Biostructure and Bioimaging, National Research Council
Via Tommaso De Amicis 95, 80145 Napoli - Italy

Corresponding author:
Raffaele Liuzzi, Ph.D
Institute of Biostructure and Bioimaging, National Research Council
Via Tommaso De Amicis, 95 80145 Naples, Italy
tel. +39.081.2203187 ext 229 Fax +39.081.2296117
e-mail: raffaele.liuzzi@cnr.it
Point by point revision

**Reviewer 1**

Mayor points:
Points 1,2,3: abstract was changed

Point 4, 10: The use of sensitivity and specificity of CCSVI in MS as measures of its impact of the disease are an accepted extension of their original statistical meaning, as already done in Zivadinov R et al.: *Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS*. Neurology 2011, 77(2):138-44. Moreover, by using the same analysis we aimed to produce results comparable with previous published ones. We kept the table unchanged also on the basis of the editor suggestion (see decision letter).

Point 5: we agree that it can be a results of selection bias with a probability of 0.1%, as implicit in the statistical significance of the test. Regarding Bastianello et al hypothesis it arises from a not blinded and with no healthy controls study and with a very low inter-center concordance and it is not corroborated by any other controlled study result.

On the congenital nature of CCSVI we agree that there are some data on a precocious presence of venous abnormalities [7,12], but data are extremely contrasting and our results do not point towards such a conclusion. Only longitudinal and preclinical studies can elucidate the temporary relation of CCSVI with MS.

Point 6: we modified this section of discussion. We agree that there are no proves for IJV extrinsic compression but we cannot exclude such hypothesis, extrapolating the evidences of lower limbs. We implemented references accordingly [26,27].

Point 7: we believe data the absence of such correlation in HC might depend on the small number of subjects in this group (power= 30%), as we added in discussion.

Point 8: there are some evidences of structural valve disease secondary to inflammatory mediated endothelial damage [37]. We implemented discussion with pathophysiological hypothesis and related references.

Point 9: we changed the conclusions.

Minor points:
Point 12: abstract was changed accordingly

Point 13: since we did not have venography results, we limited our study on sonographic evidences.

Point 14: genetically related and unrelated meant relatives or not relatives of MS patients. We changed in the text.

Point 15: criteria were Zamboni ones, as we explained in methods. We added this specification more often in the text.
Point 16: by CCSVI status we meant presence or absence of CCSVI. We changed status into presence.

Point 17: we referred to EDSS Functional Systems, as usually assessed in MS patients by neurologists, now we explained it more exhaustively in methods and results.

Point 18: increased was changed into higher.

Point 19: study was changed into review.

Point 20: indeed we refer to hemodynamic alterations, not to established CCSVI, in the elderly.

Point 21: flux detectable by Eco Colour Doppler.

Point 22: we corrected the citation style and number.

Point 23: we added some references.

Point 24: we changed the grouping of the bars. As regards to the bars orientation we think, according to Cleveland WS (Cleveland WS, 1984, The American Statistician), that the differences among horizontal bars are easier to read than that among vertical bars.

Point 25: we corrected the truncated legend.

Point 26: English was improved.

Reviewer 2

Major points:
Point 1: we changed the abstract accordingly.

Point 2: we agree that more sophisticated techniques and longitudinal studies are necessary to sort out the relationship of CCSVI and MS especially in earlier stages of disease. We added some comments in discussion.

Point 3: we realize that there are reports of CCSVI also in pediatric MS and at onset of disease, but our results are contrasting. We added a comment on this point in discussion and the paper by Baracchini et al on CCSVI prevalence at MS onset in the references.

Point 4: we changed the conclusions and added some references.

Minor points:
Point 1: we changed the title accordingly.

Point 2: we updated the introduction regarding hypoperfusion.

Point 3: we cannot exclude such a correlation and we added a comment in discussion.


