Reviewer's report

Title: Clinical Correlates of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis

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Reviewer: Brenda Banwell

Reviewer's report:

Weinstock-Guttman et al describe the relationship between clinical MS disease course and disease severity and findings related to CCSVI. The following are comments or suggestions for the authors:

1. In the Abstract, the sentence beginning with “This analysis…” is unclear, as it does not indicate whether the authors are referring to the current manuscript or the manuscript discussed in the sentence prior. The concluding statement of the abstract is also misleading. The correlations between CCSVI is not with “presentation” (as this often refers to initial manifestations)- rather it is with current MS disease state (relapsing, secondary progressive, or primary progressive course).

2. It is unclear why the authors elected to retain the 21 CIS patients and 10 pediatric MS patients. Neither group is discussed in any detail subsequently. Of the 21 CIS participants, how many meet the 2010 MS diagnostic criteria? How many have isolated optic neuritis (with normal brain MRI) or other demyelinating presentations with a lower likelihood of future confirmation of MS? If the CIS group are truly a mixed population with variable likelihood of future MS diagnosis, the added value of including them is questionable. The pediatric patients should either be discussed or removed.

3. The authors are reporting a clinical paper. Yet they do not address important clinical variables that could influence venous flow, such as any relationships between CCSVI or any specific component and (i) blood pressure; (ii) concurrent medications (especially antihyptertensives or other vasoactive medications; (iii) fluid status at the time of ultrasound (were participants instructed on consumption of fluids prior to ultrasound?); or (iv) smoking.

4. The authors should remove any mention of “cure” in the introduction. Such statements are inappropriate in any context relating to CCSVI.

5. The authors use the term “venous anomalies” frequently. Most people reserve such a term for structural abnormalities. While some aspects of ultrasound findings in the CCSVI analyses do discuss venous valve abnormalities and structural narrowing, other components relate solely to venous flow. Flow findings would not be an “anomaly” in most contexts.

6. In the Analysis section, the sentence beginning with “Multinomial logistic….“ is unclear. What is “Control-Non-progressive MS-Progressive”? 
7. How were “relapsing” vs “non-relapsing” SPMS and PPMS patients defined? What was the time interval from last relapse that led to consideration of a patient being “non-relapsing”?

8. Despite an association between SPMS and PPMS and CCSVI, the EDSS score was not correlated. This important discrepancy should be further discussed.

9. Most of the Discussion either repeats the authors prior findings, or focuses on theories for CCSVI that were not evaluated by the authors nor supported by any literature. All such text is extraneous to the present study and should be removed (first 3 paragraphs and paragraph 5). The paragraph on spinal cord ANM (based on a single article from 1950) seems completely irrelevant. References 8 and 9 are not research studies exploring spinal vasculature and do not support the statements made by the authors that congestive myelopathy is a true pathological entity.

10. All comments on “progressive worsening” of VH criteria also are inaccurate. The authors performed a cross-sectional study—serial analyses are required to substantiate that findings are retained or worsen over time. The final paragraph mentions the need for prospective serial studies, but as written suggests that the authors have already evaluated progression. The more precise statement is that the authors have compared the frequency of CCSVI features in patients with relapsing MS to those of patients with progressive forms of the disease.

11. Reference 25 is incomplete.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I am a principal investigator of a funded study of CCSVI.