RESEARCH LETTER

Cerebral and Cervical Venous Outflow Abnormalities Are Dynamic

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t was recently proposed that inflammation associated with multiple sclerosis (MS) is caused by chronic cerebrospinal venous insufficiency (CCSVI) owing to chronically elevated cerebral venous pressure that leads to disruption of the blood-brain barrier and entry of inflammatory mediators into the central nervous system.1 The results of the original studies1 that reported CCSVI in 100% of patients with MS (as demonstrated by specific venous ultrasonography abnormalities) have not consistently been replicated using sonography,2–6 magnetic resonance venography,7,8 or selective venography.9 Intracranial pressure measurements in patients with MS are no different from control subjects.9 In a 2011 study of US veterans with MS, we failed to show any association between cerebral venous ultrasonography abnormalities and MS.10 There was no significant difference between the number of ultrasonography abnormalities found in patients with MS compared with control subjects. In addition, none of the study subjects fulfilled criteria of CCSVI, defined as 2 or more ultrasonography abnormalities by proponents of the controversial CCSVI theory.1 Overall, currently there appears to be no scientific evidence to support CCSVI as an etiologic factor in MS. Nevertheless, both patients and practitioners continue to promote it and treat it as if it were.

One possible reason to explain conflicting results from different research studies is the potentially low reliability and reproducibility of venous ultrasonography assessments owing to the plasticity of these vessels. We hypothesized that repeat studies would show intrapersonal variations with regard to venous diameter and blood flow. Therefore, all 8 study subjects of our original investigation10 with any abnormal ultrasonography results within the cervical or cerebral veins—including patients with a clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS, or primary progressive MS—and healthy control subjects were reevaluated to determine whether the original findings could be replicated. Both the ultrasonography technician and interpreter were blinded to the subjects’ diagnosis. The ultrasonography technician did not have access to original study results, which were available to the ultrasonography interpreter. All repeat ultrasonography studies were normal (Table).

These observations indicate that cerebral and cervical venous abnormalities as detected by ultrasonography may not always be persistent structural abnormalities and may further weaken the association of singular abnormal imaging findings and MS.

Table. Results of Repeat Ultrasonography in Individuals Positive for CCSVI Criteria

<table>
<thead>
<tr>
<th>Ultrasonography Findings</th>
<th>Subjects With Original Assessment</th>
<th>Subjects With Repeat Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux IJV/VV</td>
<td>0/29</td>
<td>0/8</td>
</tr>
<tr>
<td>Reflux DCV</td>
<td>1/29 (1 SPMS case)</td>
<td>0/8</td>
</tr>
<tr>
<td>IJV Stenosis</td>
<td>0/29</td>
<td>0/8</td>
</tr>
<tr>
<td>Absent flow IJV/VV</td>
<td>3/29 (1 SPMS case; 2 control subjects)</td>
<td>0/8</td>
</tr>
<tr>
<td>Negative change in CSA</td>
<td>4/29 (2 SPMS cases; 2 control subjects)</td>
<td>0/8</td>
</tr>
</tbody>
</table>

Abbreviations: CCSVI, chronic cerebrospinal venous insufficiency; CSA, cross-sectional area; DCV, deep cerebral vein; IJV, internal jugular vein; SPMS, secondary progressive multiple sclerosis; VV, vertebral vein.

*All 8 study subjects of our original investigation with any abnormal ultrasonography results within the cervical or cerebral veins—including patients with a clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS, or primary progressive MS—were reevaluated to determine whether the original findings could be replicated. All repeat ultrasonography studies were normal.

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Author Contributions: Study concept and design: Marder, Gupta, and Stuve. Acquisition of data: Marder, Gupta, Ragland, and Stuve. Analysis and interpretation of data: Marder and Stuve. Drafting of the manuscript: Marder, Ragland, and Stuve. Critical revision of the manuscript for important intellectual content: Gupta and Stuve. Statistical analysis: Marder and Stuve. Administrative, technical, and material support: Marder, Gupta, Ragland, and Stuve. Study supervision: Gupta and Stuve.

References:
In an analysis of prospectively collected observational data, Gao et al. found that statin use was associated with a lower risk for incident Parkinson disease. This benefit with statins was apparent only in subjects younger than 60 years at baseline and only with at least 6 years of use. I suggest an interpretation of these findings that Gao et al. did not consider. Parkinson disease is a neurodegenerative disorder that does not develop overnight. There may be a window of opportunity for modification of the disease process, and this window may close as age advances. Expressed otherwise, the onset of neurodegenerative changes is more likely in older subjects, and once these changes are even subclinically established, it may be too late for statins to prevent the eventual clinical appearance of the disorder.

In this context, I wonder whether more than 6 years of treatment with statins, which was found to be protective, was a proxy for an earlier initiation of use; that is, initiation of use within the window of opportunity.

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In reply

We thank Dr. Andrade for his comments on our study of statin use and risk for Parkinson disease (PD),1 which to be clear demonstrated an association rather than a protective effect. We agree that PD has a long preclinical stage and that early interventions are more likely to modify the disease process.

In our previous studies, we observed that several pre-Parkinson symptoms (eg, constipation, weight loss, and erectile dysfunction) preceded the onset of motor symptoms.2-4 Hyposmia and REM sleep behavior disorder have been also consistently found to be able to predict future PD risk.5,6 These signs may contribute to the early identification of individuals at risk for PD and eventually improve disease treatment and prevention.

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