

ONLINE FIRST

No Cerebral or Cervical Venous Insufficiency in US Veterans With Multiple Sclerosis

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Objective: To determine if chronic cerebral venous insufficiency exists in patients with multiple sclerosis (MS) using ultrasonography and 4-dimensional color Doppler ultrasonography examination and unverified criteria proposed by Zamboni et al.

Design: Patients with MS and clinically isolated syndrome were matched by age and sex with subjects with migraine or no neurological disease. All subjects underwent gray-scale, color, and spectral Doppler ultrasonography examination of the internal jugular veins (IJVs), vertebral veins, and deep cerebral veins for stenosis, absence of signal, and reflux.

Setting: Academic MS center.

Patients: All patients with MS fulfilled revised McDonald criteria for the diagnosis of MS. Patients with clinically isolated syndrome exhibited a typical transient focal neurological deficit and had magnetic resonance imaging

lesions typical of MS. Control subjects were recruited from the VA migraine clinic or staff.

Main Outcome Measures: Five parameters of venous outflow used by Zamboni et al were examined: (1) IJV or vertebral vein reflux, (2) deep cerebral vein reflux, (3) IJV stenosis, (4) absence of flow in IJVs or vertebral veins, and (5) change in cross-sectional area of the IJV with postural change.

Results: There was no significant difference in the number and type of venous outflow abnormalities in patients with MS compared with controls.

Conclusion: This study does not support the theory that chronic cerebral venous insufficiency exists in MS.

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MULTIPLE SCLEROSIS (MS) is an inflammatory demyelinating and degenerative disease of the central nervous system (CNS).¹ The cause of MS is unknown. Although MS may affect any part of the CNS, perivenous inflammation and demyelination have long been recognized as the histopathological signature of the disorder.¹ Evidence suggests that this microscopically conspicuous profile signifies disruption of the blood-brain barrier associated with an immune response that is either the initial cause of the MS lesion or secondary to another immunogenic event within the CNS.^{2,3}

*For editorial comment
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Several recently published studies suggest that the perivenous inflammation and perhaps the disease itself are initiated by cerebral venous hypertension or chronic cerebrospinal venous insufficiency

(CCSVI).⁴⁻⁸ According to a hypothesis proposed by Zamboni and colleagues,⁷ elevated cerebral venous pressure due to vascular abnormalities such as venous stenosis or valve incompetence cause impaired venous drainage and as a result cerebral venous hypertension. The increased pressure mechanically disrupts the blood-brain barrier allowing blood to enter the brain and initiate, or participate in, an inflammatory response.

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This novel hypothesis is the result of several studies in patients with MS using Doppler and transcranial color-coded Doppler ultrasonography.⁴⁻⁷ These investigators reported that impairment of cerebrospinal venous drainage due to venous stenosis or valvular incompetence was present by ultrasonography in 100% of patients with MS studied but not in any subjects without MS.⁷ In another study, Zamboni et al⁹ report disease phenotype-specific venous

outflow characteristics in patients with MS. Finally, the same investigators suggest that surgically correcting the stenosis identified by ultrasonography has a beneficial effect on the MS disease course.¹⁰

Other investigators have not been able to reproduce the findings published by Zamboni et al. In 1 recent study, using ultrasonographic criteria of CCSVI proposed by Zamboni et al,⁷ venous anomalies were found in a small number of both patients with MS and control subjects by extracranial and transcranial color-coded ultrasonography without significant differences between the 2 groups.¹¹

The purpose of this study was to reproduce recent ultrasonography observations made by Zamboni and co-workers in US veterans of the armed forces with MS.

METHODS

SUBJECTS AND CLINICAL ASSESSMENTS

This study was approved by the Dallas, Texas, VA Medical Center Internal Review Board, and informed consent was obtained from all subjects.

ULTRASONOGRAPHY STUDIES

All examinations were performed with a phased-array ultrasonography system (Logic 9; GE Healthcare, Milwaukee, Wisconsin) equipped with 8-MHz linear and 2-MHz sector transducer probes. For extracranial evaluation, an 8-MHz transducer was used and for transcranial evaluation, a 2-MHz probe. B-mode, gray-scale, color Doppler, and spectral Doppler ultrasonography were used while interrogating each vein. Each subject was investigated first in the supine and then in an upright (90°, sitting) position, after end inspiration and end expiration. Studies were performed by an ultrasonographer blinded to subject diagnosis and interpreted by a radiologist blinded to subject diagnosis.

Specifically, 5 criteria defined by Zamboni et al necessary for the diagnosis of CCSVI, and which purportedly increase cerebral venous pressure, were investigated: (1) reflux more than 88 seconds in the internal jugular veins (IJVs) and/or vertebral veins (VVs), (2) reflux in the deep cerebral veins (DCVs), (3) B-mode evidence of proximal IJV stenosis, defined as local reduction of the cross-sectional area (CSA) of 50% or more in the supine position (0°), (4) flow not Doppler detectable in both IJVs and/or both VVs, and (5) missing IJV diameter decrease in the sitting position, ie, reverted postural control of the main cerebral venous outflow pathways.⁷

Extracranial assessment of the bilateral IJVs and VVs was performed after inspiration and expiration with subjects at 0° and 90° with respect to the normal plane. Patency of these veins was assessed first by insonating their entire accessible length using the sagittal and transverse planes. The presence of possible occlusion and stenosis in these veins was investigated. Occlusion was defined as when the vein was seen on gray-scale imaging; however, there was no Doppler-detectable flow. The stenosis was defined as a local CSA reduction of 50% or more, following the suggestion of Zamboni et al. Cross-sectional area, blood volume flow, and blood flow velocity were recorded in these veins in the upper region of the neck close to the mandibular angle. The CSA was measured in transverse plane on the gray-scale image, assuming a circular shape to the vessel. Flow direction in these vessels was studied with both color Doppler and spectral Doppler. The presence of reflux in these veins,

signifying a flow reversal from its physiological direction for a duration of more than 0.88 second, was studied.

Transcranial assessment of the intracranial venous vasculature was performed following established criteria for transcranial color-coded duplex ultrasonography. Both transtemporal and transoccipital approaches were used in this study. With the transtemporal approach, DCVs were identified on each side and analyzed in both 0° and 90° positions during inspiration and expiration. Similarly, with the transoccipital approach, the transverse sinus (TS) was analyzed on each side. Blood volume flow and blood flow velocity were recorded in these veins in each position during end inspiration and end expiration. Physiological intracranial venous flow is unidirectional. As per criteria used by Zamboni et al, bidirectional flow was assessed when, in at least 1 of these postural conditions, flow reversal was less than 0.5 second and for venous reflux, when the flow reversal was more than 0.5 second.

STATISTICAL METHODS

The sample size was based on 2 power analyses. One analysis was performed using the percentage of differences between groups in the Zamboni et al study⁹ and the other, using their odds ratio of 43. Based on these calculations, it was determined that 6 patients with MS and 6 controls were required to achieve a power of 0.90 with an $\alpha = .05$. These requirements were met and exceeded in this study. Pearson χ^2 tests were used to test our null hypothesis, namely that the frequency distribution of venous ultrasonography characteristics as defined by Zamboni et al⁷ in our population was consistent with those observed by Zamboni et al. Correlations between continuous and categorical variables were assessed using the Mann-Whitney *U* test. *P* values $< .05$ were considered significant.

RESULTS

PATIENTS

Eighteen patients (3 women and 15 men) with a diagnosis of definite MS fulfilling revised McDonald criteria¹² or clinically isolated syndrome (CIS) were recruited from the VA MS clinic and included in the study. The mean (SD) age of the patients was 55.2 (11.6) years. Six patients had relapsing-remitting MS, 1 had CIS, 10 patients had secondary progressive MS, and 1 patient had primary progressive MS. Patients who had had a relapse or received steroids in the last 30 days were excluded from the study.

Eleven age- and sex-matched subjects (4 women and 7 men) with migraine headaches or individuals without a neurological diagnosis were recruited as a reference population. The mean (SD) age of the reference group was 55.3 (11.1) years. Subjects with a history of cerebral venous thrombosis, transient global amnesia, thrombosis of the jugular vein(s), central venous catheter in the IJV, head and neck surgery, or heart or lung disease were not eligible for this study.

There was also no significant difference between the patients with MS and the control subjects with respect to age ($z = 0.24$; $P = .82$) or sex ($\chi^2_1 = 1.2$; $P = .26$). The results for specific criteria as defined by Zamboni et al are shown later. Demographics of patients with MS and controls are summarized in **Table 1**.

Table 1. Demographics of Patients With MS and Controls^a

Subjects	Sample Size	Age, y Mean (SD)	Sex (F/M)	Disease Duration, y, Median
Patients with MS	18	55.2 (1.6)	3/15 (82.4% M)	20.8 (2-40)
RRMS	6			12.5 (2-29)
SPMS	10			23.9 (11-40)
CIS	1			10 ^b
PPMS	1			20 ^b
Controls	11	55.3 (11.1)	4/7 (63.6% M)	NA

Abbreviations: CIS, clinically isolated syndrome; MS, multiple sclerosis; NA, not applicable; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

^aThe Mann-Whitney *U* test showed no significant difference between patients with MS and controls in age ($z=0.24$; $P=.82$). The χ^2 test showed no significant difference between the groups in sex ($\chi^2=1.2$; $P=.26$).

^bOne patient only.

Table 2. CCSVI Criteria^a

CCSVI Criteria	No./Total No. of Subjects				
	Reflux IJV/VV	Reflux DCV	IJV Stenosis	Absent Flow IJV/VV	Negative Change in CSA
RRMS	0/6	0/6	0/6	0/6	0/6
SPMS	0/10	1/10	0/10	1/10	2/10
CIS	0/1	0/1	0/1	0/1	0/1
PPMS	0/1	0/1	0/1	0/1	0/1
Controls	0/11	0/11	0/11	2/11	2/11

Abbreviations: CCSVI, chronic cerebrospinal venous insufficiency; CIS, clinically isolated syndrome; CSA, cross-sectional area; DCV, deep cerebral vein; IJV, internal jugular vein; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; VV, vertebral vein.

^aThe χ^2 test showed no significant difference between patients with MS and controls ($\chi^2 = 1.2$; $P = .26$).

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The total examination time was approximately 60 minutes in each subject. Insonation of the TSs was not performed in 1 patient with MS; the right TS was not seen in 1 patient with MS. In 1 control subject, the DCV and TS were not seen on either side; in 1 control subject, the TS was not seen on either side; in 1 control subject, the left TS was not seen; and in 1 control subject, the left VV was not seen.

ZAMBONI CRITERIA 1 TO 5 IN PATIENTS WITH MS AND CONTROL SUBJECTS

Of the 18 patients with MS, 4 patients met 1 definition for CCSVI proposed by Zamboni and coworkers.⁷ In 2 patients, there was a negative change in the left IJV CSA. There was reflux in the right TS in 1 patient. No left VV flow was detected in 1 patient. Among the 11 control subjects, 4 met 1 definition for CCSVI proposed by Zamboni and coworkers. Two individuals displayed a negative change in CSA in the left IJV. No right VV flow was seen in 1 control and no flow in the left VV was seen in 1 control. There was no significant difference in the number of ultrasonography abnormalities between patients with MS and controls (**Table 2**).

Zamboni Criterion 1

Cerebral or cervical venous reflux more than 88 seconds was not detected in the IJVs or VVs of either patients with MS or control subjects.

Zamboni Criterion 2

Reflux in DCVs was found in 1 patient with secondary progressive MS.

Zamboni Criterion 3

High-resolution B-mode evidence of proximal IJV stenosis, defined as local reduction of CSA of 50% or more in the supine position, was not detected in any subjects.

Zamboni Criterion 4

Flow not Doppler detectable was found in 1 VV of 1 patient with secondary progressive MS and 2 controls.

Zamboni Criterion 5

Negative change in CSA in the IJV from supine to sitting position (reverted postural control) was found in 2 patients with secondary progressive MS and 2 control subjects.

COMMENT

This study failed to detect a significant difference in the Zamboni et al criteria for impairment to cerebral venous drainage in patients with MS compared with control subjects. A number of investigators have attempted to reproduce the Zamboni et al results using their criteria and methods.^{11,13-16}

The earliest clinical event in patients with MS is termed a *clinically isolated syndrome*. If CCSVI plays a pathogenic role in MS, one would expect to see evidence of it at disease onset. Baracchini et al¹⁵ performed transcranial-extracranial Doppler with high-resolution color-coded duplex ultrasonography on 50 patients with CIS at high risk for conversion to MS, as well as 50 age- and sex-matched controls. A total of 8 of 50 patients (16%) with CIS fulfilled CCSVI criteria. In addition, 7 of 8 patients with CIS underwent selective venography of the IJVs and azygos veins. In 6 of 7 of these patients, there was normal or regular IJV and azygos drainage. The remaining patient had right IJV hypoplasia. Ultrasonography criteria for CCSVI abnormalities were not confirmed on venography, suggesting ultrasonography may not be an accurate method for identification of venous abnormalities.

Zivadinov and colleagues¹³ studied 499 subjects, 289 with MS, 163 healthy controls, 260 with other neurological diseases, and 21 patients with CIS. The CCSVI criteria were met by subjects in all groups (56.1% with MS, 42.3% with other neurological diseases, 38% with CIS, and 22.7% healthy controls). Despite the significantly higher incidence of CCSVI in patients with MS that was detected in this study, it is substantially lower than the 100% incidence found by Zamboni et al. Based on these findings, the presence of CCSVI is neither sensitive nor specific for MS. Furthermore, 20% of subjects had no DCV assessment because of failure to identify these structures or the presence of artifact, suggesting that ultrasonography in this study, or more likely in general, is unreliable and subjective as a method for the study of CCSVI.

Doepf et al¹¹ studied 56 patients with MS (41 with relapsing-remitting MS and 15 with secondary progressive MS) and 27 age- and sex-matched controls. No subjects fulfilled CCSVI criteria (≥ 2 of the 5 Zamboni et al ultrasonography criteria), and there was no difference in the number of (single) abnormalities in subjects with MS vs controls.

Centonze et al¹⁶ studied 140 subjects, 84 patients with MS and 56 healthy controls, using the Zamboni et al method for identification of CCSVI and ultrasonography technicians and interpreters trained by Zamboni. This study showed no significant difference in CCSVI frequency between patients with MS and healthy controls. In addition, there was no difference in patients with MS and evidence of CCSVI compared with patients with MS without evidence of CCSVI with respect to disease progression or severity.

Perhaps the most reliable and validated measurement of venous pressure is by venous intraluminal catheter. Zamboni et al performed selective venography in all 65 patients with MS and 48 of 235 controls and measured venous pressure.¹³ These investigators reported no significant difference in venous pressure measured in patients and controls.

Meyer-Schwickerath and coworkers¹⁴ used ophthalmodynamometry to measure intracranial venous pressure in 29 patients with MS, 28 healthy controls, and 19 patients with documented elevated intracranial pressure. All patients with MS and control subjects

had normal venous pressures. Only cases with intracranial pressure pathology had elevated venous pressures. In addition, ultrasonography appears to be an unreliable method for the detection of cerebrospinal venous abnormalities due to either technical factors or subjectivity.

Current treatments for MS are only partially effective, some aimed at suppressing inflammation by broadly modulating or suppressing the immune system and others, by preventing inflammatory cells from entering the CNS through a disrupted blood-brain barrier. The most effective treatments have a potential risk of serious morbidity and even mortality. We welcome new insights into the disease process and especially the promise of a single effective treatment. However, our findings and those of other investigators call into question whether CCSVI plays a pathogenic role in a substantial fraction of patients with MS and whether it presents a valid therapeutic target. The results presented herein refute that hypothesis and corroborate those of other investigators who have recently been unable to replicate the Zamboni et al observations.

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