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Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS



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ABSTRACT

Background: Chronic cerebrospinal venous insufficiency (CCSVI) was recently described in patients with multiple sclerosis (MS). A subject is considered CCSVI positive if ≥ 2 venous hemodynamic (VH) criteria are fulfilled.

Objective: To determine prevalence of CCSVI in a large cohort of patients with MS, clinically isolated syndrome (CIS), other neurologic diseases (OND), and healthy controls (HC), using specific proposed echo-color Doppler (ECD) criteria.

Methods: Transcranial and extracranial ECD were carried out in 499 enrolled subjects (289 MS, 163 HC, 26 OND, 21 CIS). Prevalence rates for CCSVI were calculated in 3 ways: first, using only the subjects for whom diagnosis was certain (i.e., borderline subjects were excluded); secondly, including the borderline subjects in the "no CCSVI" group; and finally, taking into account subjects who presented any of the VH criteria.

Results: CCSVI prevalence with borderline cases included in the "no CCSVI" group was 56.1% in MS, 42.3% in OND, 38.1% in CIS, and 22.7% in HC ($p < 0.001$). The CCSVI prevalence figures were 62.5% for MS, 45.8% for OND, 42.1% for CIS, and 25.5% for HC when borderline cases were excluded ($p < 0.001$). The prevalence of one or more positive VH criteria was the highest in MS (81.3%), followed by CIS (76.2%), OND (65.4%), and HC (55.2%) ($p < 0.001$). CCSVI prevalence was higher in patients with progressive than in nonprogressive MS ($p = 0.004$).

Conclusions: Our findings are consistent with an increased prevalence of CCSVI in MS but with modest sensitivity/specificity. Our findings point against CCSVI having a primary causative role in the development of MS. *Neurology*® 2011;77:000-000

GLOSSARY

CCSVI = chronic cerebrospinal venous insufficiency; **CIS** = clinically isolated syndrome; **CTEVD** = Combined Transcranial and Extracranial Venous ECD Evaluation; **ECD** = echo-color Doppler; **EDSS** = Expanded Disability Status Scale; **HC** = healthy control; **MRV** = magnetic resonance venography; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **NPV** = negative predictive value; **OND** = other neurologic disease; **OR** = odds ratio; **PPMS** = primary progressive multiple sclerosis; **PPV** = positive predictive value; **PRMS** = progressive-relapsing multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis; **VH** = venous hemodynamic criteria.

Multiple sclerosis (MS) is considered an autoimmune disease of the CNS characterized by inflammation, demyelination, and neurodegeneration.¹ Recently, a strong association between MS and a condition defined as chronic cerebrospinal venous insufficiency (CCSVI) was reported.²

CCSVI was described as a vascular condition characterized by anomalies of the main extracranial cerebrospinal venous routes that interfere with normal blood outflow in patients with MS.²⁻⁴ Several recent studies have shown that venous anomalies may be present in the internal jugular veins, the vertebral veins, and the azygous vein, and can be detected by selective venography,^{2,3,5} extracra-

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From the Buffalo Neuroimaging Analysis Center (R.Z., K.M., C.K., M.E., J.R., C.B., K.H., M.A., E.C., M.G.D.), The Jacobs Neurological Institute, Department of Neurology, University at Buffalo (R.Z., M.R., R.H.B.B., A.E.Y., D.H., B.W.-G.), and Department of Pharmaceutical Sciences (M.R.), State University of New York, Buffalo; and Department of Biostatistics (G.C.), University of Alabama, Birmingham.

Study funding: Supported by internal resources of the Buffalo Neuroimaging Analysis Center and Baird MS Center, the Jacobs Neurological Institute, University of Buffalo; the Direct MS Foundation; the Jacquemin Family Foundation; and smaller donors. The results from the CTEVD study led to the organization of the IRB-approved (HSIRB NEU2860310E), unblinded, open-label descriptive study into CCSVI that includes patients with either possible or definite MS. The purpose of this fee-for-service registry study is to enhance utilization of data on venous anomalies that are obtained on individuals who have sought information on CCSVI status.

Disclosure: Author disclosures are provided at the end of the article.

nial venous echo-color Doppler (ECD),²⁻⁷ and with lower sensitivity and specificity by magnetic resonance venography (MRV).⁵ However, other recent studies were not able to reproduce these findings.⁸⁻¹⁰

Combined transcranial and extracranial ECD allows for noninvasive assessment of venous hemodynamic (VH) parameters indicative of CCSVI.^{2,4-7} These ECD parameters were classified into 5 VH criteria.² Two or more abnormal VH ECD criteria were used as a cutoff for CCSVI diagnosis classification on an individual subject basis.² Presence of CCSVI was never observed in 235 controls, but perfectly overlapped with the diagnosis of clinically definite MS in 65 patients with MS.^{2,3}

The Combined Transcranial and Extracranial Venous ECD Evaluation (CTEVD) study was designed to determine the prevalence of CCSVI in a large cohort of patients with MS, clinically isolated syndrome (CIS), other neurologic diseases (OND), and healthy controls (HC), using specific proposed ECD criteria.²

METHODS This single-center, cross-sectional, rater-blinded study included 500 subjects. Inclusion criteria were adult or pediatric patients with possible or definite MS, including those with CIS, relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), progressive-relapsing MS (PRMS), and neuromyelitis optica (NMO), and adult or pediatric HC, or controls with OND. The HC group included genetically related and genetically unrelated subjects. Exclusion criteria were presence of relapse and steroid treatment in the 30 days preceding study entry for all patients, preexisting medical conditions known to be associated with brain pathology (e.g., cerebrovascular disease, positive history of alcohol abuse) in HC, contraindications for having a contrast agent injected for MRI examination, history of cerebral congenital vascular malformations (Klippel-Trenaunay, Parkes-Weber, Servelle-Martorell, Budd-Chiari syndromes), and pregnancy. Additional ECD-related exclusion criteria are listed in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

The patients with OND had the following diseases: antiphospholipid syndrome (5), Hashimoto encephalopathy (3), acute disseminated encephalomyelitis (2), Parkinson disease (2), and 1 case each of systemic lupus erythematosus, trigeminal neuralgia, migraine, headache, myelopathy, fibromyalgia, Sjögren syndrome, neurosarcoidosis, chronic immune optic neuritis, vertigo, dementia, degenerative disc disease, chronic inflammatory demyelinating polyneuropathy, and complete transverse myelitis.

The ECD evaluators were blinded to the subjects' status. The ECD personnel were unaware of how many patients with MS, OND, or CIS and HC were assessed until study enrollment was closed. As in any case-control study that includes disabled patients vs HCs, blinding was a challenge in the CTEVD study. We aimed to ensure proper blinding by adopting the following strategies: 1) instructing subjects not to reveal their disease status

during the ECD examination; 2) including patients with CIS and patients with early RRMS with no disability or walking difficulties to ensure blinding between nondisabled patients with MS and HC; 3) including patients with OND who presented with gait disturbances and incoordination, dysarthria, and memory problems similar to those of patients with MS, which provided blinding for the disabled patients with MS; and 4) using an ECD technologist unfamiliar with the signs and symptoms of either MS or OND.

The same blinding procedures were applied for the intrarater reproducibility study in relation to disease status at baseline. In order to ensure proper follow-up blinding, the CCSVI status from both scanning sessions was determined after the follow-up examination was completed.

Study assessments. Participants underwent a clinical examination and transcranial and extracranial ECD scans of the head and neck. Standard demographic and clinical information on all participating subjects were acquired via a structured questionnaire and by examination. This included but was not limited to age, sex, age at disease onset, age at diagnosis, symptoms at disease onset and diagnosis, disease duration, Expanded Disability Status Scale (EDSS),¹¹ disease subtype,¹² physical examination with measurement of blood pressure, detailed medical history of vascular risks with particular emphasis on venous diseases, familial history, relapse history, information about laboratory examinations at symptom onset, and current and previous therapy information.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local Institutional Review Board (HSIRB #NEU2490109A), and informed consent was obtained from all subjects.

ECD evaluation. The specific details of equipment, subject length of examination, contraindications and limitations, specific Doppler parameters, criteria definitions, description of probes, positioning of the subject, techniques used, fulfillment of VH criteria, and pathology definitions are provided in appendices e-1 and e-2.

We focused on the detection of 5 anomalous VH criteria affecting cerebrospinal venous return, as previously described² (appendix e-1).

All study examinations in the CTEVD study were performed by the same ECD technologist (K.M., with 25+ years of vascular ultrasound experience) who was trained for several weeks prior to start of the study. All examinations were overread by a certified neuroimager (D.H.).

Intrarater reproducibility for CCSVI status was assessed on 28 subjects (14 HC, 11 MS, and 3 OND) who were examined in a blinded manner twice over a 1-week period. The agreement was 89.3% between the 2 measurements (κ 0.75, $p < 0.001$, 95% confidence interval 0.48–1.0). In total, the CCSVI classification status of 3 of the 28 subjects changed at the follow-up examination; one case was classified as borderline at baseline and as abnormal at follow-up, one case as normal at baseline and abnormal at follow-up, and one case as abnormal at baseline and normal at follow-up.

CCSVI status assessment. Each subject was assigned a total criteria VH score which was calculated by counting the number of criteria that the subject fulfilled. A subject was considered CCSVI-positive if ≥ 2 VH criteria were fulfilled, as previously proposed.² Subjects who were not assessed for a VH criterion due to the lack of assessment or technical issues were assumed not to have fulfilled that criterion.

Table 1 Demographic and clinical characteristics of the enrolled disease groups^a

	MS disease courses									
	HC (n = 163)	CIS (n = 21)	OND (n = 26)	All MS (n = 289)	NMO (n = 6)	PPMS (n = 11)	PRMS (n = 1)	RRMS (n = 191)	Relapsing SPMS (n = 19)	Nonrelapsing SPMS (n = 61)
Age, y, median (IQR) ^b	47 (18.5)	38 (11)	50 (21.5)	48 (16)	48.5 (10.8)	54 (10.5)	46 (–)	44 (16.5)	55 (10.5)	55 (12)
% Male	46.0	33.3	26.9	23.5	16.7	45.5	0	23.6	5.3	26.2
M/F	75 ^c /88	7/14	7/19	68/221	1/5	5/6	0/1	45/146	1/18	16/45
EDSS, median (IQR)		1.5 (1)		3.0 (4)	5.0 (2.3)	6.0 (2)	3.5 (–)	2.0 (1.5)	5.5 (2)	6.0 (1.3)
No. missing		2		17		2		13		2
Disease duration, y, median (IQR) ^d		4 (6)	5 (9.5)	12 (13)	10.5 (3.8)	15 (9.5)	13 (–)	10 (11)	18 (23)	20 (16)

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HC = healthy controls; IQR = interquartile range; MS = multiple sclerosis; NMO = neuromyelitis optica; OND = other neurologic disease; PPMS = primary progressive multiple sclerosis; PRMS = progressive-relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

^a Of the 289 patients with MS, 257 were on disease-modifying therapy. These included 86 patients on interferon β -1a IM, 26 on interferon β -1a SC, 1 on interferon β -1b, 64 on glatiramer acetate, 55 on natalizumab, 7 on IV immunoglobulin, 5 on mycophenolate mofetil, 3 on azathioprine, 3 on combination therapy, 1 on mitoxantrone, and drug data for 6 patients were not recorded.

^b Defined as age at Doppler visit.

^c Includes one transgendered male.

^d Defined as the difference between age at Doppler visit and age at onset.

Because of this, subjects who were not assessed for all 5 VH criteria were classified in 3 subgroups: 1) no CCSVI group—subjects who presented 4 negative VH criteria, and even if these subjects had been assessed for the missing VH criterion and found to fulfill this criterion, these subjects still would not have been diagnosed with CCSVI; 2) CCSVI group—subjects who fulfilled at least 2 of the other 4 criteria, and assessment of the missing VH criterion would not change their classification; 3) borderline CCSVI group—subjects who fulfilled exactly one of the other 4 criteria and would need to be assessed for the missing VH criterion before they could be classified as presenting CCSVI or not.

Prevalence rates for CCSVI were calculated in 3 ways: first, using only the subjects for whom diagnosis was certain (i.e., borderline subjects were excluded); secondly, including the borderline subjects in the no CCSVI group; and finally, taking into account subjects who presented any of the VH criteria.

Statistical analyses. Statistical analyses were performed using Statistical Analysis Software (SAS, version 9.2). For descriptive statistics and estimates of prevalence, *t* tests, Fisher exact tests, and χ^2 tests were used. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and relative odds ratio (OR) between HC and patients with MS were calculated using logistic regression techniques and direct computation from 2 \times 2 tables. Prevalence rates for each of the 5 criteria, as well as for different CCSVI status groups, were calculated. In order to avoid too many spurious findings due to multiple comparisons, we do not report anything as statistically significant unless the nominal *p* value was <0.01 by using 2-tailed tests.

RESULTS Demographic and clinical characteristics. Of the 500 enrolled subjects, 499 subjects were eligible for statistical analysis: 163 HC, 289 MS, 21 CIS, and 26 OND. One patient with MS with SP disease

subtype was inadvertently screened twice and, therefore, only the first of his assessments was included in the analysis. No subjects were excluded due to ECD-related exclusion criteria (appendix e-1). Table 1 shows demographic and clinical characteristics of the enrolled disease groups. There was a higher proportion of males in the HC group compared to the other study groups ($p < 0.001$), stemming largely from the spouse controls. No age, sex, or disease duration differences were found in any of the control or disease groups in subjects either with or without the presence of CCSVI (data not shown). Ten pediatric patients with MS were included. The mean age of the pediatric MS cases was 16 years (SD 3, minimum 9 and maximum 17 years). Of the 289 patients with MS, 257 were on disease-modifying therapy (table 1).

CCSVI status assessment. Table 2 shows the CCSVI classifications by disease group. CCSVI classification was related to disease group ($p < 0.001$). Of the 499 examined subjects, 374 subjects were assessed on the 5 CCSVI criteria; the remaining 125 subjects were assessed on only VH criteria 1, 3, 4, and 5. For the 125 subjects who were not assessed on VH criterion 2, 42 were classified in the no CCSVI group, 31 in the CCSVI group, and the remaining 52 subjects in the borderline CCSVI group. The reasons for nondiagnostic assessment of VH criterion 2 were nonvisualization of deep cerebral veins in 52 (41.6%) subjects and presence of artifact (scatter, clutter, speckle, or aliasing) in 86 (68.8%) subjects. Thirteen

Table 2 CCSVI classification by disease group

Classification	Disease group, n (%)				
	HC	CIS	OND	MS	Total
CCSVI	37 (22.7)	8 (38.1)	11 (42.3)	162 (56.1)	218 (43.7)
No CCSVI	108 (66.3)	11 (52.4)	13 (50)	97 (33.5)	229 (45.9)
Borderline	18 (11)	2 (9.5)	2 (7.7)	30 (10.4)	52 (10.4)
Total	163	21	26	289	499

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; CIS = clinically isolated syndrome; HC = healthy controls; MS = multiple sclerosis; OND = other neurologic disease.

subjects presented 2 reasons for nondiagnostic assessment of VH criterion 2 (nonvisualized in one position and an artifact in the other position). Noise interference was not detected in any subject. Prevalence rates for VH criterion 2 are based only on the 374 subjects who were assessed for this criterion. Prevalence rates for CCSVI were assessed on 447 subjects for whom diagnosis was certain, and then by including the borderline subjects in the no CCSVI group.

Prevalence rates in study groups. Table 3 shows prevalence rates by disease group according to the individual VH criterion. CCSVI prevalence with borderline cases included in the no CCSVI group was 56.1% in MS, 42.3% in OND, 38.1% in CIS, and 22.7% in HC ($p < 0.001$). The CCSVI prevalence figures were 62.5% for MS, 45.8% for OND, 42.1% for CIS, and 25.5% for HC when borderline cases were excluded ($p < 0.001$). The prevalence of one or more positive VH criteria was the highest in MS (81.3%), followed by CIS (76.2%), OND (65.4%), and HC (55.2%) ($p < 0.001$).

Table 4 shows the CCSVI classifications for patients with MS separated by subtype of MS. There

was a trend for relationship between CCSVI classification and disease subtype ($p = 0.033$). When the borderline cases were included in the no CCSVI group, the highest prevalence was seen in relapsing SPMS (89.4%), followed by nonrelapsing SPMS (67.2%), NMO (66.6%), PPMS (54.5%), and RRMS (49.2%). Post hoc analysis showed that patients with MS with progressive (relapsing and nonrelapsing SPMS, PPMS, and PRMS) disease subtype had higher CCSVI prevalence than those with nonprogressive (RR) MS ($p = 0.004$).

Table e-1 shows the CCSVI classification for patients with MS separated by age group (adult vs pediatric MS). No relationship was found between CCSVI classification and age group ($p = 0.894$).

Table e-2 provides the CCSVI classifications for genetically related and unrelated HC. CCSVI classification was not related to genetic status ($p = 0.627$).

Sensitivity, specificity, PPV, and NPV between patients with MS and HC. Table 5 shows the OR for patients with MS as compared to HC for each of the 5 criteria and for various CCSVI status definitions. When the borderline cases were included in the no CCSVI group, sensitivity was 56.1%, specificity was 77.3%, PPV was 81.4%, NPV was 49.8%, and OR was 4.33 ($p < 0.001$).

DISCUSSION Our findings are consistent with increased prevalence of CCSVI in MS, but substantially lower than the originally reported sensitivity/specificity rates in MS.^{2,4} There were differences between the groups studied, with patients with MS showing the highest CCSVI prevalence compared to HC, patients with CIS, or patients with OND. The CCSVI prevalence was higher in patients with progressive MS and patients with NMO than in patients with RRMS or patients with CIS.

Table 3 Prevalence rates by disease group, n (%)

	HC, yes/total	CIS, yes/total	OND, yes/total	MS, yes/total	p Value ^a
VH criterion 1	33/163 (20.2)	7/21 (33.3)	4/26 (15.4)	130/289 (45)	<0.001
VH criterion 2	15/118 (12.7)	6/14 (42.9)	7/20 (35.0)	104/222 (46.8)	<0.001
VH criterion 3	63/163 (38.7)	12/21 (57.1)	12/26 (46.2)	185/289 (64)	<0.001
VH criterion 4	12/163 (7.4)	0/21 (0)	7/26 (26.9)	30/289 (10.4)	0.014
VH criterion 5	11/163 (6.7)	2/21 (9.5)	2/26 (7.7)	33/289 (11.4)	0.449
CCSVI ^b	37/145 (25.5)	8/19 (42.1)	11/24 (45.8)	162/259 (62.5)	<0.001
CCSVI ^c	37/163 (22.7)	8/21 (38.1)	11/26 (42.3)	162/289 (56.1)	<0.001
≥1 VH positive criterion	90/163 (55.2)	16/21 (76.2)	17/26 (65.4)	235/289 (81.3)	<0.001

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; CIS = clinically isolated syndrome; HC = healthy controls; MS = multiple sclerosis; OND = other neurologic disease; VH = venous hemodynamic criteria.

^a p Value for Fisher exact test for independence represents comparison among all 4 groups. The p value for CCSVI^b between MS vs HC was <0.001, between MS vs OND was 0.131, and between HC vs OND was 0.39.

^b Borderlines excluded.

^c Borderlines included in the no CCSVI group.

Table 4 CCSVI classification by MS subtype, n (%)^a

	NMO	PPMS	PRMS	RRMS	Relapsing SPMS	Nonrelapsing SPMS	Total
CCSVI	4 (66.7)	6 (54.5)	0	94 (49.2)	17 (89.5)	41 (67.2)	162 (56.1)
No CCSVI	2 (33.3)	4 (36.4)	1 (100)	74 (38.7)	2 (10.5)	14 (23)	97 (33.5)
Borderline	0	1 (9.1)	0	23 (12.1)	0	6 (9.8)	30 (10.4)
Total	6	11	1	191	19	61	289

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; MS = multiple sclerosis; NMO = neuromyelitis optica; PPMS = primary progressive multiple sclerosis; PRMS = progressive-relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

^a There was a trend for relationship between CCSVI classification and disease subtype ($p = 0.033$). Post hoc analysis showed that patients with MS with progressive (relapsing and nonrelapsing SPMS, PPMS, and PRMS) disease subtype had higher CCSVI prevalence than those with nonprogressive (RR) MS ($p = 0.004$).

Given the recent interest in the CCSVI hypothesis as a possible cause of MS, independent evaluation of CCSVI has been identified as an urgent need. Our results indicate that only 56.1% of patients with MS and 38.1% of patients with CIS presented with CCSVI (table 3). Association does not imply causality and indeed 42.3% of patients with OND and 22.7% of HC also presented with CCSVI. These findings point against CCSVI as having a primary causative role in MS.

A recent study¹³ suggested a condition similar to truncular venous malformation may cause CCSVI and may therefore be involved in the development of MS. The findings from the CTEVD study argue against such a hypothesis because: 1) 61.9% of patients with CIS at first symptom onset and 43.9% of patients with MS did not present with CCSVI; 2) 42.3% of patients with OND and 22.7% of HC presented with CCSVI. Given the composition of our OND group that was biased toward immune mediated or inflammatory diseases, we cannot exclude that prevalence of CCSVI may be increased in patients with OND presenting with similar diseases. Moreover, there was no CCSVI prevalence differ-

ence between genetically related and unrelated HC, which would argue against a genetic origin of the CCSVI hypothesis.

The prevalence of CCSVI was higher in progressive forms of MS, being the highest in relapsing SPMS (89.4%), followed by nonrelapsing SPMS and PPMS. RRMS and CIS showed the lowest prevalence. These findings suggest that CCSVI may be a consequence rather than a cause of MS. Several studies have reported hypoperfusion of the brain parenchyma of patients with MS advancing with disease progression^{14–17} and it is possible that the venous anomalies (CCSVI) may be secondary to reduced perfusion. An association between the presence and severity of CCSVI and hypoperfusion of the brain parenchyma was recently reported in a pilot study of 16 patients with RRMS.¹⁸ The role of CCSVI in contributing to or being a consequence of MS progression cannot be excluded and should be further investigated.

Of the 10 pediatric patients with MS who participated in the study, 5 presented with CCSVI (50%), yielding similar prevalence to adult patients with MS. Although the sample size is too small to make any firm conclusion, these results suggest that

Table 5 Sensitivity, specificity, positive and negative predictive value, and odds ratio between patients with MS and healthy controls

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Odds ratio (95% CI)	p Value ^a
VH criterion 1	45.0 (39.3–50.8)	79.8 (72.9–85.2)	79.8 (72.9–85.2)	45.0 (39.3–50.8)	3.21 (2.02–5.20)	<0.001
VH criterion 2	46.8 (40.4–53.4)	87.3 (80.1–92.1)	87.4 (80.2–92.2)	46.6 (40.1–53.2)	6.02 (3.24–11.87)	<0.001
VH criterion 3	64.0 (58.3–69.3)	61.3 (53.7–68.5)	74.6 (68.8–79.6)	49.0 (42.2–55.8)	2.82 (1.86–4.28)	<0.001
VH criterion 4	10.4 (7.4–14.4)	92.6 (87.6–95.7)	71.4 (56.3–82.8)	36.8 (32.3–41.6)	1.46 (0.70–3.22)	0.316
VH criterion 5	11.4 (8.3–15.6)	93.3 (88.3–96.2)	75.0 (60.5–85.4)	37.3 (32.7–42.0)	1.78 (0.85–4.02)	0.137
CCSVI ^b	62.5 (56.5–68.2)	74.5 (66.8–80.9)	81.4 (75.4–86.2)	52.7 (45.9–59.4)	4.85 (3.04–7.87)	<0.001
CCSVI ^c	56.1 (50.3–61.7)	77.3 (70.3–83.1)	81.4 (75.4–86.2)	49.8 (43.7–55.9)	4.33 (2.76–6.90)	<0.001
≥1 VH positive criterion	81.3 (76.4–85.4)	44.8 (37.4–52.5)	72.3 (67.2–76.9)	57.5 (48.8–65.7)	3.52 (2.25–5.54)	<0.001

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; CI = confidence interval; MS = multiple sclerosis; NPV = negative predictive value; PPV = positive predictive value; VH = venous hemodynamic criteria.

^a The p values refer to the significance of the odds ratios between patients with MS and healthy controls.

^b Borderlines excluded.

^c Borderlines included in the no CCSVI group.

CCSVI is also present in children and is not the result of aging.

A recent opinion paper¹⁹ identified important questions and study design issues including blinding that will need to be addressed in studies of CCSVI in MS and its role in disease etiology. Both our and the original CCSVI study,² with very different results, were blinded. Nevertheless, our findings differ most prominently from those reported previously for VH criterion 5 (table 3).² In that study,² it was found that more than 50% of their MS cohort were positive for this criterion whereas we detected only 11.4%. Although 25% of the CTEVD study cohort was not assessed for VH criterion 2, patients with MS and patients with CIS had a higher prevalence of this criterion than HC and patients with OND. We found a higher prevalence of VH criterion 3 (B-mode abnormalities) in patients with MS (64%) and patients with CIS (57.1%) than reported in the original CCSVI study (37%).²

The sensitivity, specificity, PPV, NPV, and OR figures were substantially lower in the CTEVD study compared to the initial CCSVI studies.^{2,4} The exact reasons for these differences are not clear. However, the CTEVD study included a North American population and a much larger cohort of patients with MS and HC than the original CCSVI study.² The need for training in application of the ECD CCSVI protocol has recently been emphasized.²⁰ We carefully followed the original ECD protocol after appropriate training. Nevertheless, our study showed high specificity (77.3%), high PPV (81.4%), and an OR of 4.33 for diagnosis of MS vs HC. VH criteria 2, 4, and 5 showed the highest specificity for MS. When the presence of ≥ 1 VH criteria was used to assess CCSVI, the sensitivity for patients with MS was high (81.3%) but the specificity was low (44.8%), confirming previous findings.^{2,4}

Based on our sensitivity, specificity, PPV, NPV, and OR results (table 5), it is inconclusive whether an ECD examination can be proposed as a diagnostic test for MS, as similar findings were found in patients with OND. The relatively low sample size of the OND group prevents any conclusion in that direction.

Future ECD studies should involve multiple sites to facilitate the development of standardized ECD criteria for study of venous function in MS. Our detailed protocol (appendix e-1) is an initial step in that direction.

Several recent reports have presented evidence against the CCSVI hypothesis.^{8–10} A study of 56 patients with MS and 20 HC found no differences in cerebrospinal venous drainage using transcranial and extracranial ECD.⁸ However, this study was not blinded and there were deviations from original ECD

methodology: the flow direction was assessed with the Valsalva maneuver and not by physiologic breathing.²¹

The redundancy in the venous drainage system may enable sufficient venous outflow in the presence of certain venous anomalies. The differences between our study, the original CCSVI,³ and other studies^{8–10} likewise emphasize the need for a multimodal approach for assessment of CCSVI. In addition to ECD, use of selective venography,^{2,3,5} MRV,^{5,10} phase-contrast cine-MRI,^{22,23} intraluminal Doppler methods,²⁴ intraluminal optical coherence tomography,²⁵ and pathologic approaches can provide more evidence on the existence (or not) of CCSVI in MS. Our preliminary study using MRV in 10 patients with MS and 7 HC showed that MRV has limited value for diagnosis of CCSVI. This may be due to a lack of MRV dynamism in real time and importance of morphologic, positional, and hemodynamic changes in the venous function.⁵

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DISCLOSURE

Dr. Zivadinov serves as a Section Editor for *BMC Neurology* and serves on speakers' bureaus for Biogen Idec, Teva Neuroscience, and Sanofi-Aventis. K. Marr reports no disclosures. Dr. Cutter has served on scientific advisory boards for and received funding for travel from Millenium Pharmaceuticals, Inc., Klein Buendel, Inc., Alexion Pharmaceuticals, Inc., Androclous Therapeutics, Inc., University of Illinois, Amgen, New York University, and Somnus Therapeutics, Inc.; receives royalties from the publication of *Evaluation of Health Promotion and Disease Prevention* (The McGraw Hill Companies, 1984); has received honoraria from GlaxoSmithKline, Biogen Idec, Novartis, Advanced Health Media Inc., EMD Serono, Inc., EDJ Associates, Inc., the National Heart, Lung, and Blood Institute, National Institute of Neurological Diseases and Stroke, National Marrow Donor Program, Consortium of Multiple Sclerosis Centers; serves as a consultant to Peptimmune Inc., Aegis Creative Marketing, Novartis, National Industrial Sand Association, Bayer Pharmaceuticals, and Teva Pharmaceuticals Industries Ltd.; has served on independent data and safety monitoring committees for Antisense Therapeutics Limited, Sanofi-Aventis, Bayhill Pharmaceuticals, BioMS Medical Corp, Daiichi-Sankyo Co. Inc., GlaxoSmithKline, Genmab A/S, Medivation Inc., PTC Therapeutics Inc., Teva Pharmaceutical Industries Ltd., Vivus Inc., NHLBI, NINDS, and NMSS; has received research support from ApopLogic Pharmaceuticals, LLC; receives research support from the NIH (NINDS 5U01NS042685-02 [PI]), NINDS U01 NS45719-01A1 [PI, Coordinating Center], NIAID contract no. HHSN266200400068C [coinvestigator], NHLBI 5R01 HL06991-02 [PI, Coordinating Center], NIAID N01AI30025 [Director, Coordinating Center], NIDR 3R01DE016684-03S109 [coinvestigator], NHLBI 5P50HL084923-030001 [Director, Coordinating Center], NIDDK 1R01DK078826 [coinvestigator], NIAID P30AI27767 [Co-Director, Biostatistics Core], NIDDK 1P30DK079337 [Director, Biostatistics Core], and the Consortium of Multiple Sclerosis Centers (Director NARCOMS Data Center) and the National Multiple Sclerosis Society; and serves as President of Pythagoras, Inc. Dr. Ramanathan serves on the editorial board of *The AAPS Journal*; receives royalties from the publication of *The Pharmacy Calculations Workbook* (Pinnacle, Summit and Zenith, 2008); serves as a consultant for Allergan, Inc., Biogen Idec, and Netezza Corporation; serves as a consultant for Allergan, Inc. and Biogen Idec; serves on the speakers' bureau for Biogen Idec; and receives research support from EMD Serono, Inc., Novartis, Pfizer Inc., Biogen Idec, the

US Department of Defense, and the National Multiple Sclerosis Society. Dr. Benedict serves on scientific advisory boards for Merck Serono, Biogen Idec, Bayer Schering Pharma, Novartis, and Pfizer Inc.; serves on the editorial boards of *Multiple Sclerosis*, *Neuropsychology*, and the *International Journal of MS Care*; receives royalties from Psychological Assessment Resources; has received speaker honoraria from Biogen Idec, Pfizer Inc., Abbott, Bayer Schering Pharma, Merck Serono, and Teva Pharmaceutical Industries Ltd.; receives research support from Shire plc, Biogen Idec, the NIH (3R01DC004689-08S1 [coinvestigator]), and the National Multiple Sclerosis Society; and has given expert testimony in several personal injury trials. C. Kennedy and Dr. Elfadil report no disclosures. Dr. Yeh has served as a consultant for Guidepoint Global and receives research support from the NIH (R01 NS062820-01A2 [coinvestigator]), Jog for the Jake, the Children's Guild Foundation, and the National MS Society. J. Reuther, C. Brooks, K. Hunt, M. Andrews, E. Carl, and M.G. Dwyer report no disclosures. Dr. Hojnacki serves as a consultant for Biogen Idec and on speakers' bureaus for Biogen Idec, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., and Pfizer Inc. Dr. Weinstock-Guttman serves on the Medical Advisory Board of the National Multiple Sclerosis Society; has received funding for travel and speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., and Pfizer Inc.; serves on the editorial board of *aan.com*; serves on speakers' bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., and Pfizer Inc.; serves as a consultant for Novartis and Sanofi-Aventis; and receives research support from Biogen Idec, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., Cyberonics, Inc., and the National MS Society.

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