Combined Transcranial and Extracranial Venous Doppler Evaluation (CTEVD) study.

Description of the Design and Interim Results of an Epidemiological Study of the Prevalence of Chronic Cerebrospinal Venous Insufficiency in MS and Related Diseases

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Background

- The prevailing wisdom that central nervous system damage (CNS) in multiple sclerosis (MS) is predominantly the result of abnormal immune responses against the patient's nervous tissue has been challenged recently by Zamboni et al., [1,2] who found strong associations between MS and a condition defined as chronic cerebrospinal venous insufficiency (CCSVI).
- CCSVI is a vascular condition characterized by anomalies of the main extracranial cerebrospinal (CS) venous routes that interfere with normal CS venous outflow. These anomalies affect the internal jugular veins (IJV), the vertebral veins (VV) and the azygous vein (AZY), and can be detected using selective venography and extracranial venous echo-color Doppler (ECD). [1,2]
- Combined transcranial and extracranial ECD allows for non-invasive assessment of venous hemodynamic (VH) parameters indicative of CCSVI. [1,2] CCSVI diagnosis needs to fulfill at least 2 out of 5 VH abnormal criteria. These 5 criteria include: 1) reflux in the IJVs and/or in the VVs assessed in both sitting and supine postures, 2) reflux in the deep cerebral veins (DCVs), 3) B-mode detection of stenoses in the IJVs in the form of annuli, webs, septa, or malformed valves, 4) absence of ECD signal in the IJV and/or in the VVs, even after forced deep breaths, in both sitting and supine postures, and 5) presence of a negative difference in the cross sectional area (CSA) of the IJV.
- In a previous study, ≥2 abnormal criteria in the same subject were never observed in controls, but perfectly overlapped with the diagnosis of clinically definite MS (sensitivity 100%, specificity 100%, positive predictive value (PPV) 100%, and negative predictive value (NPV) 100%).

Objective

- To ascertain the prevalence of CCSVI in a large cohort of patients with MS, healthy controls (HC) and controls with other neurological diseases (OND) using specific proposed ECD criteria. [1,2]

Methods

Design

- This single-center cross-sectional study began in April 2009 and planned to enroll 1700 consecutive subjects, including: 1000 adult patients with possible and definite MS [50 clinically isolated syndrome (CIS), 50 radiologically isolated syndrome (RIS), 500 relapsing-remitting (RR), 300 secondary-progressive (SP), 50 primary-progressive (PP) and 50 neuromyelitis optica (NMO)]. The comparison group would include 300 OND controls and 300 adult age- and sex-matched HC. Fifty pediatric patients (<18 yrs) with acquired demyelinating diseases (MS and acute disseminated encephalomyelitis) and 50 pediatric HC were also to be assessed.
- The participants were to receive a clinical examination and an ECD scan of the head and neck. In addition, all MS patients and a sub-cohort of HC and OND would have undergone brain MRI. A consecutive subgroup (MS, HC and OND) underwent an MRI of the veins of the neck to corroborate the ECD diagnosis of CCSVI.
- The ECD and MRI evaluators were completely blinded to subject status.
- Data were planned a priori to be unblinded at three predetermined time points: enrollment of 500, 1000 and 1700 subjects, respectively. The first 500 subjects included in the study were enrolled on a consecutive basis without specific matching for age, sex, disease group or MS disease course. It was originally planned that subsequent cohorts would be selected based on the total number of subjects to be enrolled in the cells and the prevalence determined based on CCSVI prevalence data derived from the first 500 enrolled subjects.
- As of 12/31/09, the enrollment of the first 500 subjects was completed.
- The prevalence of VH abnormalities identified in the different study groups was the principal endpoint of the first interim analysis.

Table 1. Demographic and Clinical Characteristics of the Enrolled Disease Groups

		MS Subtypes								
	HC (n = 163)	CIS (n = 21)	OND (n = 26)	All MS (n = 289)	NMO (n = 6)	PP (n = 11)	PR (n = 1)	RR (n = 191)	Relapsing SP (n = 19)	Non-relapsing SP (n = 61)
Age[a]										
Median	47	38	50	48	48.5	54	46	44	55	55
(IQR)	(18.5)	(11)	(21.5)	(16)	(10.8)	(10.5)	--	(16.5)	(10.5)	(12)
Sex										
% Male	46.0%	33.3%	26.9%	23.5%	16.7%	45.5%	0%	23.6%	5.3%	26.2%
Male/Female	75[b] / 88	7 / 14	7 / 19	68 / 221	1 / 5	5 / 6	0/1	45 / 146	1 / 18	16 / 45
EDSS										
Median		1.5		3	5	6	3.5	2	5.5	6
(IQR)		(1)		(4)	(2.3)	(2)	--	(1.5)	(2)	(1.3)
[# Missing]		[2]		[17]		[2]		[13]		[2]
Disease duration (years)[c]										
Median		4	5	12	10.5	15	13	10	18	20
(IQR)		(6)	(9.5)	(13)	(3.8)	(9.5)	--	(11)	(23)	(16)

[a] Defined as age at Doppler visit
[b] Includes one transgender male
[c] Defined as the difference between age at Doppler visit and age at onset

Table 2. CCSVI Classification by Disease Group

	Disease Group				
Classification	HC	CIS	OND	MS	Total
CCSVI	37	8	11	162	218
No CCSVI	108	11	13	97	229
Borderline	18	2	2	30	52
Total	163	21	26	289	499

ECD evaluation

- The CS venous return was examined using a MyLab25GOLD ECD machine (Esaote-Biosound, Italy) equipped with 2.5 and 7.5-10 Mhz transducers, with the subject positioned on a tilt bed at 90° and 0°, and the vessels insonated with an angle of 60°, as previously described. [1]
- Our chief ECD technologist, with 25+ years of vascular ultrasound experience, was trained by Prof. Zamboni in Italy/USA for several weeks prior to study start. The training involved assessment of approximately 75 MS and HC subjects who were examined in an unblinded manner. The CTEVD study was not started until sufficient experience was acquired.
- In order to ensure the consistency of our approach during the study, we used a specific phantom (GAMMEX Model 1430GS Mini Doppler Flow System, Middleton, WI, USA) for calibration purposes that was conducted every 3 months. The ECD quality control ability of the phantom examines the ECD for signal sensitivity, color flow sensitivity, flow sensitivity at depth, color flow B-mode image congruency, directional discrimination, accuracy of flow velocity readout and sample gate positioning accuracy.
- We focused on the detection of 5 anomalous VH criteria affecting CS return, as previously described. [1]

Prevalence cohort

- Of the 500 enrolled subjects, 499 subjects were eligible for statistical analysis: 163 HC, 289 MS subjects, 21 CIS and 26 subjects with OND. One MS patient with SP disease course was enrolled twice and, therefore, only one of the patient's assessments was included in the analysis. The patient presented ≥2 abnormal VH criteria on both examinations.
- Table 1 shows demographic and clinical characteristics of the enrolled disease groups.

CCSVI assessment

- 374 subjects were assessed on the five CCSVI criteria; the remaining 125 subjects were assessed on only VH criteria 1, 3, 4, and 5. Each subject was assigned a total criteria VH score which was calculated by counting the number of criteria each subject fulfilled. Subjects who were not assessed for VH criterion 2 were assumed not to have fulfilled that criterion; thus, for these subjects the total score is an underestimate of the true score.
- For the 125 subjects (45 HC, 7 CIS, 6 OND, 67 MS) who were not assessed on VH criterion 2 (technical difficulty), 42 (19 HC, 3 CIS, 3 OND, 17 MS) did not fulfill any of the other 4 criteria. Even if these subjects had been assessed for VH criterion 2 and found to fulfill this criterion, these subjects still would not be diagnosed with CCSVI. That is, despite the fact that we cannot say for sure whether the true total criteria score is zero or one, we can say with certainty that these subjects do not have CCSVI.

Table 3. Prevalence Rates by Disease Group

	HC yes/no	CIS yes/no	OND yes/no	MS yes/no	p-value[a]
Criterion 1	33 / 163 (20.2%)	7 / 21 (33.3%)	4 / 26 (15.4%)	130 / 289 (45.0%)	< .001
Criterion 2	15 / 118 (12.7%)	6 / 14 (42.9%)	7 / 20 (35.0%)	104 / 222 (46.8%)	< .001
Criterion 3	63 / 163 (38.7%)	12 / 21 (57.1%)	12 / 26 (46.2%)	185 / 289 (64.0%)	< .001
Criterion 4	12 /163 (7.4%)	0 / 21 (0.0%)	7 / 26 (26.9%)	30 / 289 (10.4%)	.014
Criterion 5	11 / 163 (6.7%)	2 / 21 (9.5%)	2 / 26 (7.7%)	33 / 289 (11.4%)	.449
CCSVI[b]	37 /145 (25.5%)	8 / 19 (42.1%)	11 / 24 (45.8%)	162 / 259 (62.5%)	< .001
CCSVI[c]	37 / 163 (22.7%)	8 / 21 (38.1%)	11 / 26 (42.3%)	162 / 289 (56.1%)	< .001
≥ 1 VH Positive Criterion	90 / 163 (55.2%)	16 / 21 (76.2%)	17 / 26 (65.4%)	235 / 289 (81.3%)	< .001

[a] p-value for Fisher's exact test for independence
[b] Borderlines excluded
[c] Borderlines included in the "No CCSVI" group

- In contrast, 31 (8 HC, 2 CIS, 1 OND, 20 MS) of the subjects who were not assessed on VH criterion 2 fulfilled at least 2 of the other 4 criteria. We can say with certainty that these subjects present CCSVI.
- The remaining 52 subjects (18 HC, 2 CIS, 2 OND, 30 MS) fulfilled exactly one of the other 4 criteria and would need to be assessed for VH criterion 2 before they can be diagnosed. We refer to these cases as "borderline."
- Prevalence rates for each of the 5 criteria, as well as for CCSVI, were calculated. Prevalence rates for VH criterion 2 are based only on the 374 subjects who were assessed for this criterion. Prevalence rates for CCSVI were calculated in 2 ways: first, using only the 447 subjects for whom diagnosis was certain (i.e., borderline subjects were excluded), and then by including the borderline subjects in the "No CCSVI" group.

Results

Prevalence rates

- Table 2 shows the CCSVI classifications by disease group. CCSVI classification was significantly related to disease group (p< .001 from Fisher's exact test).
- Table 3 shows prevalence rates by disease group according to the single VH criterion, CCSVI groups in which borderline cases were excluded or included and according to those who presented with ≥ 1 VH positive criteria.
- Table 4a shows the CCSVI classifications for MS patients separated by age group. No significant relationship was found between CCSVI classification and age group (p = .894 from Fisher's exact test).
- Table 4b shows the CCSVI classifications for MS patients separated by type of MS. CCSVI classification was significantly related to disease subtype (p = .033).
- Table 4c gives the CCSVI classifications for the familial and non-familial HC. CCSVI classification was not significantly related to familial status (p = .627).

Comparison between MS patients and HC

- Table 5 shows the odds ratios for MS as compared to HC for each of the 5 criteria and CCSVI. Sensitivity, specificity, positive predictive value, and negative predictive value for using these criteria to predict MS are also given.

Conclusion

- Our findings are consistent with increased prevalence of CCSVI in MS but lower than the originally reported sensitivity/specificity rates in MS.
- Further blinded studies are needed to determine prevalence of CCSVI in MS.

Disclosure

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Table 4a. CCSVI Classification by Age Group for MS patients

	MS - Adult	MS - Pediatric	Total
CCSVI	157	5	162
No CCSVI	93	4	97
Borderline	29	1	30
Total	279	10	289

Table 4b. CCSVI Classification by MS Subtype

	NMO	PP	PR	RR	Relapsing SP	Non-relapsing SP	Total
CCSVI	4	6	0	94	17	41	162
No CCSVI	2	4	1	74	2	14	97
Borderline	0	1	0	23	0	6	30
Total	6	11	1	191	19	61	289

Table 4c. CCSVI Classification by Familial Status

	Familial HC	Non-familial HC	Total
CCSVI	13	24	37
No CCSVI	31	77	108
Borderline	4	14	18
Total	48	115	163

Table 5. Comparison between MS and HC

	Sensitivity (95% C.I.)	Specificity (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)	Odds Ratio (95% C.I.)	p-value
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)	< .001
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)	< .001
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)	< .001
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)	.316
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)	.137
CCSVI[a]	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)	< .001
CCSVI[b]	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)	< .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)	< .001

[a] Borderlines excluded
[b] Borderlines included in the "No CCSVI" group

References

1. Zamboni, P., Galeotti, R., Menegatti, E., et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
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