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ORIGINAL RESEARCH

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BACKGROUND AND PURPOSE: CCSVI has been reported to occur at high frequency in MS. Its significance in relation to MR imaging parameters also needs to be determined, both in patients with MS and HCs. Therefore, this study determined the associations of CCSVI and conventional MR imaging outcomes in patients with MS and in HCs.

MATERIALS AND METHODS: T2, T1, and gadolinium lesion number, LV, and brain atrophy were assessed on 3T MR imaging in 301 subjects, of whom 162 had RRMS, 66 had secondary-progressive MS subtype, and 73 were HCs. CCSVI was assessed using extracranial and transcranial Doppler evaluation. The MR imaging measure differences were explored with 27 borderline cases for CCSVI, added to both the negative and positive CCSVI groups to assess sensitivity of the results of these cases.

RESULTS: No significant differences between subjects with and without CCSVI were found in any of the individual diagnostic subgroups or MS disease subtypes for lesion burden and atrophy measures, independently of the CCSVI classification criteria used, except for a trend for higher T2 lesion number (irrespective of how borderline cases were classified) and lower brain volume (when borderline cases were included in the positive group) in patients with RRMS with CCSVI. No CCSVI or MR imaging differences were found between 26 HCs with, or 47 without, a familial relationship.

CONCLUSIONS: CCSVI is not associated with more severe lesion burden or brain atrophy in patients with MS or in HCs.

ABBREVIATIONS: CCSVI = chronic cerebrospinal venous insufficiency; CIS = clinically isolated syndrome; CTEVD = Combined Transcranial and Extracranial Venous Doppler; EDSS = Expanded Disability Status Scale; HC = healthy control; LV = lesion volume; RRMS = relapsing-remitting MS; SPMS = secondary-progressive MS

MS is primarily considered a chronic inflammatory disease of the CNS characterized by inflammation, demyelination, and neurodegeneration, mediated mainly by T- and B-cells.[1]

CCSVI has been reported to occur at high frequency in MS.[2,3] CCSVI was originally 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]

The concept of CCSVI in patients with MS, and its possible implications for MS pathogenesis and treatment options, has raised significant interest in both the patient[5] and medical communities.[6-8] Some recent studies were able to partially reproduce original findings[2-4] with substantially lower sensitivity and specificity for MS,[9-17] while others were not able to support these findings using various imaging techniques.[18-29]

In the CTEVD study,[13] the largest case-control study, to date, to investigate the prevalence of CCSVI in patients with MS, CIS, and other neurologic diseases, and HCs using specific proposed Doppler sonography criteria,[3] increased prevalence of CCSVI in MS was shown but with modest sensitivity and specificity. Despite the currently ongoing debate about whether CCSVI is associated with MS or not,[30] its significance in relation to MR imaging parameters also needs to be determined, both in patients with MS and HCs. In this study, the associations between the presence of CCSVI and conventional MR imaging measures (lesion burden and brain atrophy) in a large cohort of patients with MS and HCs has been investigated.

Materials and Methods

This study was a single-center, cross-sectional, observer-masked study that included 499 subjects.[13] Inclusion criteria for this study were patients with RRMS and secondary-progressive disease course, or HCs, having an MR imaging examination performed within 30 days of Doppler examination with the standardized study protocol. Exclusion criteria were presence of relapse and steroid treatment in the 30 days preceding study entry for all patients, pre-existing medical conditions known to be associated with brain pathology (eg, cerebrovascular disease, positive history of alcohol abuse), known history of cerebral congenital vascular malformations, and pregnancy. HCs were recruited from the following volunteer sources: hospital person-

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nel, respondents to a local advertisement, and spouses or relatives of the patients with MS. HCs needed to complete a health screening questionnaire containing information about medical history (illnesses, surgeries, medications, etc) and needed to meet the health-screen requirements on physical examination.

Participants underwent a clinical and MR imaging examination and transcranial and extracranial Doppler scans of the head and neck. Standard demographic and clinical information on all participating subjects was acquired via a structured questionnaire and by examination. The Doppler evaluators were blinded to the subjects' status, as previously described.[13] In particular, subjects were specifically instructed not to reveal their disease status during the Doppler examination. Patients with other neurologic diseases and CIS were not part of this CTEVD MR imaging substudy but were used as part of the overall population to ensure blinding in the CTEVD study. The MR imaging evaluators were completely blinded to subject disease and clinical and CCSVI status. The study was approved by the local institutional review board and informed consent was obtained from all subjects.

Doppler Sonography

The Doppler examination was performed by using MyLab 25 Gold sonography machine (Esaote, Indianapolis, Indiana) equipped with 2.5 and 7.5–10 MHz transducers and motorized chair capable of tilting from 0° to 90°. All study examinations were performed by the same Doppler technologist. We examined Doppler parameters that detect 5 anomalous venous hemodynamic criteria affecting cerebrospinal venous return. More specific discussions on subject, length of examination, contraindications and limitations, specific Doppler parameters, criteria definitions, description of probes, positioning of the subject, techniques used, fulfillment of venous hemodynamic criteria and pathology definitions is provided elsewhere.[13]

Each subject was assigned a total venous hemodynamic criteria score, calculated by counting the number of criteria that the subject fulfilled. A subject was considered CCSVI-positive if ≥2 venous hemodynamic criteria were fulfilled, as previously proposed.[3] Subjects who were not assessed for a venous hemodynamic criterion, due to technical difficulty, were assumed not to have fulfilled that criterion.[13] Subjects who fulfilled exactly 1 of the other 4 criteria and were not assessed on 1 venous hemodynamic criterion were classified as CCSVI-borderline.[13]

MR Imaging Acquisition and Analysis

All subjects were examined on a 3T Signa Excite HD 12.0 Twin Speed 8-channel scanner (GE Healthcare, Milwaukee, Wisconsin). The following sequences were acquired: 2D multiplanar dual FSE proton-attenuation and T2WI; FLAIR; 3D high-resolution T1WI using fast-spoiled gradient echo with magnetization-prepared inversion recovery pulse; spin-echo T1WI, both with and without a single dose intravenous bolus of 0.1 mMol/Kg gadolinium-diethylene triamine pentaacetic acid, 5 minutes after injection (only in patients with MS).

One average was used for all pulse sequences. All sequences were acquired with a 256 × 192 matrix (freq × phase) and FOV of 25.6 cm × 19.2 cm (256 × 256 matrix with phase FOV = 0.75), for an in-plane resolution of 1 mm × 1 mm. For all 2D scans (proton-attenuation/T2, FLAIR, and spin-echo T1), 48 sections were collected, with a thickness of 3 mm, and no gap between sections. For the 3D high-resolution inversion recovery fast-spoiled gradient echo, 128 locations were acquired, 1.5 mm thick. Other relevant parameters were as follows: for dual FSE proton-attenuation/T2, TE1/TE2/TR = 9 /98/5300 ms, flip angle = 90, echo-train length = 14; for FLAIR, TE/TI/TR = 120/2100/8500 ms (TI-inversion time), flip angle = 90, echo-train length = 24; for spin-echo T1WI, TE/TR = 16/600 ms, flip angle = 90; and for 3D high-resolution T1WI, TE/TI/TR = 2.8/900/5.9 ms, flip angle = 10. Scans were prescribed in an axial-oblique orientation, parallel to the subcallosal line.

Lesion Measures. The T2-, T1-, and gadolinium number and LVs were measured using a semiautomated edge detection contouring/thresholding technique previously described.[31]

Global and Regional Atrophy Measures. For brain extraction and tissue segmentation into gray matter and white matter, the SIENAX cross-sectional software tool was used (version 2.6; www.fmrib.ox.ac.uk/fsl/siena), with corrections for T1-hypointensity misclassification by using an in-house developed in-painting program.[32] Normalized volumes of the whole brain, gray matter volume, cortical volume, and white matter volume were assessed as previously described.[33] In addition, we calculated central atrophy measures, including normalized lateral ventricle volume and third ventricle width.[34]

Statistical Analyses

Statistical analyses were performed using the R software package (version 2.8.1; http://www.r-project.org) and SAS (version 9.3; SAS, Cary, North Carolina). For comparing demographic, clinical, and MR imaging characteristics between the study groups, *t* tests, Fisher exact tests, and χ^2 tests were used. For MR imaging measures that were based on volumes (LVs and SIENAX normalized volumes), the cube root was taken before conducting statistical analyses. The MR imaging volumetric results are expressed in milliliters.

To test the impact of the CCSVI-borderline cases on the MR imaging findings, the differences were explored with the borderline cases for CCSVI first analyzed in the negative group and then the analyses repeated, including them in the positive CCSVI group.

Due to multiple comparisons, a nominal *P* value <.01 was considered statistically significant using 2-tailed tests.

Results

Demographic and Clinical Characteristics

In total, 301 (60.3%) patients were included in this MR imaging substudy. Of the 499 subjects participating in the study, 361 (72.3%) subjects had an MR imaging examination performed with the standard MR imaging study protocol. The other 138 (27.7%) subjects did not undergo an MR imaging examination with the standard study protocol, mostly because of lack of scanner availability within the time recruitment window. Of the 361 subjects who underwent MR imaging with the standard study protocol, 10 (2.8%) subjects had MR imaging scans of insufficient quality to perform quantitative analysis. For simplicity, subgroups too small to include as separate categories in this study were excluded, as per inclusion criteria. These were 20 patients with CIS, 18 with other neurologic diseases, 10 with primary-progressive MS, 1 with progressive-relapsing disease, and 1 with neuromyelitis optica. The median number of days between Doppler sonography and MR imaging examination was 2 (minimum = 0, maximum = 30).

Demographic and clinical characteristics of the MR imaging participants are presented in Table 1. Of the 73 HCs participating in this MR imaging substudy, 27 (37%) were recruited from hospital personnel and/or local advertisement,

Table 1: Demographic and clinical characteristics of the enrolled disease group subtypes

	HC ($n = 73$)	RRMS ($n = 162$)	SPMS ($n = 66$)
Age, median (IQR)	44 (17)	44 (16)	54.5 (9)
Sex			
% Male	45.2	22.8	19.7
Male/female	33/40	37/125	13/53
EDSS, median (IQR) [# missing]		2 (1.5) [8]	6 (2) [2]
Disease duration, years; median (IQR)		9 (11)	19.5 (18)

Note:—Of the 228 patients with MS, 204 were on disease-modifying therapy. These included 68 patients on interferon beta-1a I.M., 23 on interferon beta 1a S.C., 1 on interferon beta 1b, 46 on glatiramer acetate, 50 on natalizumab, 3 on intravenous immunoglobulin, 4 on mycophenolate mofetil, 2 on azathioprine, 2 on combination therapy, and 1 on mitoxantrone; drug data for 4 patients were not recorded. IQR indicates interquartile range.

20 (27.4%) were spouses of patients with MS, and 26 (35.6%) were relatives of the patients. There were significantly more females in the MS compared with the HC group ($P = .002$); however, no sex differences were observed between the sources of HC recruitment ($P = .66$). As expected, secondary-progressive patients had higher age, disease duration, and EDSS scores (all $P < .0001$) compared with the RRMS group.

There were no significant age, sex, disease duration, or EDSS differences between those who were enrolled in this MR imaging substudy of the CTEVD ($n = 301$) and those who were not ($n = 198$; data not shown).

CCSVI Status Assessment

Of the 73 HCs, 19 (26%) were CCSVI-positive and 6 (8.2%) were CCSVI-borderline. No significant differences in CCSVI status were found with respect to the source of HC recruitment (familial versus spouse versus other). No significant age or sex differences in respect to CCSVI status were found in HCs.

Of the 228 patients with MS, 131 (57.5%) were CCSVI-positive and 21 (9.2%) were CCSVI-borderline. The figures were 81 (50%) and 19 (11.7%) in the RRMS, and 50 (75.8%) and 2 (3.2%) in the SPMS groups ($P = .001$). In patients with MS, there was no significant difference in mean age (46.3 versus 44.8 years; $P = .39$), sex ratio (77.8% versus 78.4% female; $P = .53$), or disease duration (14.6 versus 13.2 years; $P = .35$) between subjects with CCSVI and those without.

Lesion Number and Volume Differences According to the CCSVI Status

On-line Tables 1 and 2 show lesion number and LV differences by individual diagnostic subgroups according to CCSVI status, in which the borderline cases were included in the negative or positive CCSVI groups. No significant differences were found between CCSVI-positive and -negative subjects for lesion number and LV (T2, T1, and gadolinium) in individual diagnostic subgroups or MS disease subtypes, except for a trend for higher T2 lesion number in patients with RRMS with CCSVI compared with those without (CCSVI-borderline included in the positive CCSVI group, $P = .04$, and CCSVI-borderline included in the negative CCSVI group, $P = .05$).

No lesion differences were observed, according to CCSVI status, in 47 nonfamilial versus 26 familial HCs.

Global and Regional Atrophy Differences According to the CCSVI Status

On-line Tables 3 and 4 show global and regional atrophy differences by individual diagnostic subgroups according to CCSVI status, in which the borderline cases were included in the negative or positive CCSVI groups. No significant differences were found between CCSVI-positive and -negative subjects for global and regional atrophy measures in individual diagnostic subgroups or MS disease subtypes, except for a trend for lower normalized volume of the whole brain in patients with RRMS with CCSVI compared with those without, when CCSVI-borderline cases were included in the positive CCSVI group ($P = .06$).

No atrophy differences were observed, according to CCSVI status, in 47 nonfamilial versus 26 familial HCs.

Discussion

This is the first large study to investigate the relationship between extracranial venous hemodynamic alterations and intracranial MS pathology, as assessed by conventional MR imaging measures. The presence of CCSVI was not significantly related to more severe lesion burden and brain atrophy in individual diagnostic subgroups or MS disease subtypes.

A case-control rater-blinded study showed that there is an increased prevalence of CCSVI in MS, but with modest sensitivity and specificity.[13] In this MR imaging substudy, 60.3% of the participating subjects, who received standardized 3T MR imaging, were included. Similar prevalence rates of CCSVI in this MR imaging substudy were found, as in the previous study.[13]

A number of recent reports have presented evidence against the CCSVI hypothesis in MS.[18-29] The possible reasons for the discrepancies in findings between different studies are numerous.[30] Veins have a tendency to collapse and change their morphology and size. Because of this, it is complex to study the intracranial and cervical venous systems, regardless of the imaging technique used. No established standardized guidelines for detection of extracranial venous abnormalities indicative of CCSVI currently exist, though there is common knowledge among radiologists about how to perform diagnostic imaging and intervention on the extracranial veins However, the value of Doppler sonography, in properly trained hands, for screening of CCSVI was tested against reference-standard catheter venography in 2 recent pilot studies in patients with MS and HCs, with promising results.[10,35] In one of these studies, Doppler sonography showed 82% sensitivity and 100% specificity compared with catheter venography in 10 patients with MS.[35] In another recent study, using 2 different noninvasive imaging techniques, it was shown that patients with progressive MS presented with significantly more extraluminal Doppler sonography abnormalities and more flow abnormalities on MR venography than patients with nonprogressive MS.[14] A multimodal approach is recommended to determine whether CCSVI exists and to what extent it is present in various healthy and disease groups, and MS subtypes.[30]

Recent opinion papers[6,7] have discussed the urgent need to demonstrate whether the presence of CCSVI in MS may be related to disease etiology and severity, including MR imaging outcomes. At this time, it is unknown whether altered ex-

tracranial venous hemodynamic outflow may contribute to inflammatory/neurodegenerative damage in MS. No association was found between CCSVI status in individual diagnostic subgroups or MS disease subtypes, independent of whether CCSVI-borderline cases were included in the negative or positive CCSVI groups. Only patients with RRMS showed a trend for a higher number of T2 lesions among patients with CCSVI, independent of the CCSVI-borderline classification. These findings warrant further investigation but firmly suggest that if CCSVI contributes to higher lesion burden in patients with MS, then this effect is probably weak, given the relatively large MS sample size used for this MR imaging substudy (228 patients with MS). No lesion burden differences were found in patients with SPMS, both with and without CCSVI, suggesting that if CCSVI contributes to more progressive disease, then this effect is not mediated by the relationship between CCSVI and accumulation of inflammatory lesions.

Although we did not find a relationship between age and the diagnosis of CCSVI either in HCs or in the entire MS group, it cannot be excluded that the prevalence of these abnormalities is aging-dependent. A recent study that investigated internal jugular vein changes with aging in HCs found a decreased proportion of venous drainage and increased internal jugular vein reflux prevalence in older subjects.[36] Even more recently, the same group of investigators showed that subjects with severe internal jugular vein reflux had more severe age-related WM changes on MR imaging, especially in caudal brain regions.[37] Therefore, the effect of CCSVI-related abnormalities in relation to WM changes in the brain parenchyma has to be further investigated.

No significant differences in global or regional atrophy measures were found between those with and without the presence of CCSVI, independent of whether CCSVI-borderline cases were included in the negative or positive CCSVI groups. Only patients with RRMS showed a trend for lower whole-brain volume among patients with CCSVI, when CCSVI-borderline cases were included in the CCSVI-positive group. Therefore, we did not confirm results of a previous small pilot study where we found a significant relationship between a higher number of pathologic venous hemodynamic criteria and decreased brain volume.[38]

While fulfillment of ≥2 CCSVI-proposed Doppler criteria reflects the present definition of CCSVI,[3] it does not reflect its severity. To decrease the number of comparisons between the study groups with respect to their MR imaging outcomes, we decided to use only the CCSVI status in our analyses. This conservative approach should have avoided possible over-interpretation of the study findings.

No significant differences in age, CCSVI status, and source of recruitment were found between men and women in the HC group. Neither were there detected significant differences in CCSVI status and MR imaging characteristics between the HCs who presented with familial MS and those with nonfamilial MS. The results of these analyses are in line with those reported in the previous study,[13] and are corroborated by the lack of strong associations between CCSVI and HLA DRB1*1501,[39] which suggests that the role of the underlying genetic associations of CCSVI should be interpreted with caution.

There are number of potential limitations of this study. There were significantly fewer women in the HC group compared with patients with MS. Of the 499 subjects participating in the study, 39.7% were excluded in this MR imaging substudy. This is mostly because of lack of scanner availability within the time recruitment window, and because the analysis was restricted to subject groups with substantial sample size, to enable analyses comparable between the groups, and consequently smaller MS disease subgroups were excluded.

Conclusions

The lack of association between CCSVI and lesion burden and brain atrophy findings, signatures of the inflammatory and neurodegenerative processes, point against CCSVI having an important role in the accumulation of lesion burden and brain atrophy in patients with MS or in HCs.

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