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Magnetic Resonance Imaging / Formation image de résonance magnétique

## Prevalence of Extracranial Venous Narrowing on Magnetic Resonance Venography is Similar in People With Multiple Sclerosis, Their Siblings, and Unrelated Healthy Controls: A Blinded, Case-Control Study

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### Abstract

**Purpose:** The study sought to assess and compare the prevalence of narrowing of the major extracranial veins in subjects with multiple sclerosis and controls, and to assess the sensitivity and specificity of magnetic resonance venography (MRV) for describing extracranial venous narrowing as it applies to the chronic cerebrospinal venous insufficiency theory, using catheter venography (CV) as the gold standard.

**Methods:** The jugular and azygos veins were assessed with time-of-flight MRV in this assessor-blinded, case-control study of subjects with multiple sclerosis, their unaffected siblings, and unrelated controls. The veins were evaluated by diameter and area, and compared with CV. Collateral vessels were also analyzed for maximal diameter, as a potential indicator of compensatory flow.

**Results:** A high prevalence of extracranial venous narrowing was demonstrated in all study groups, collectively up to 84% by diameter criteria and 90% by area, with no significant difference between the groups when assessed independently ( $P = .34$  and  $.63$ , respectively). There was high interobserver variability in the reporting of vessel narrowing ( $\kappa = 0.32$ ), and poor vessel per vessel correlation between narrowing on MRV and CV ( $\kappa = 0.064$ ). Collateral neck veins demonstrated no convincing difference in maximum size or correlation with jugular narrowing.

**Conclusion:** There is a high prevalence of narrowing of the major extracranial veins on MRV in all 3 study groups, with no significant difference between them. These findings do not support the chronic cerebrospinal venous insufficiency theory. Although MRV has shown a high sensitivity for identifying venous narrowing, time-of-flight imaging demonstrates poor interobserver agreement and poor specificity when compared with the gold standard CV.

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## Résumé

**Objet :** La présente étude vise à évaluer et à comparer la prévalence de rétrécissement des grandes veines extra-crâniennes chez les personnes atteintes de sclérose en plaques et chez des cas témoins. Elle vise également à mesurer la sensibilité et la spécificité de la phlébographie par résonance magnétique pour la caractérisation de la sténose veineuse extra-crânienne (dans le contexte de la théorie de l'insuffisance veineuse céphalorachidienne chronique) en se servant de la phlébographie par cathétérisme comme modalité de référence.

**Méthodes :** Dans le cadre de cette étude de cas témoins menée à l'aveugle, les veines jugulaires et azygos de personnes atteintes de sclérose en plaques, de leurs frères et sœurs non touchés par la maladie et de cas témoins sans lien de parenté avec les personnes atteintes ont été évaluées au moyen d'une phlébographie par résonance magnétique par temps de vol. Les veines ont été examinées en fonction du diamètre et de la région. Les résultats ont ensuite été comparés à ceux obtenus au moyen de la phlébographie par cathétérisme. Le diamètre maximal des vaisseaux collatéraux a également été analysé, en tant que possible indicateur de débit compensatoire.

**Résultats :** Les groupes étudiés ont tous affiché une prévalence élevée de sténose des veines extra-crâniennes. À l'échelle collective, celle-ci pouvait atteindre 84 % par rapport au critère du diamètre et 90 % par rapport au critère de la région. Les groupes n'ont affiché aucune différence notable quand ils ont été évalués individuellement ( $p = 0,34$  et  $0,63$ , respectivement). La déclaration de sténose veineuse a considérablement varié d'un observateur à l'autre ( $\kappa = 0,32$ ). À l'échelle du vaisseau, aucune véritable corrélation n'a pu être établie entre un rétrécissement observé par phlébographie par résonance magnétique et un rétrécissement observé par phlébographie par cathétérisme ( $\kappa = 0,064$ ). De plus, le diamètre maximal des veines collatérales du cou n'a pas varié de façon concluante et n'a pu être corrélé avec le rétrécissement de la veine jugulaire.

**Conclusions :** La phlébographie par résonance magnétique a montré une prévalence élevée de rétrécissement des grandes veines extra-crâniennes chez les trois groupes à l'étude, mais aucune différence notable entre ceux-ci. Ces résultats n'appuient pas la théorie de l'insuffisance veineuse céphalorachidienne chronique. La phlébographie par résonance magnétique affiche un degré de sensibilité élevé pour la détection d'une sténose veineuse. Toutefois, le degré de concordance interobservateur et la spécificité de la technique par temps de vol sont faibles comparativement à ceux de la phlébographie par cathétérisme (modalité de référence).

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*Key Words:* Chronic cerebrospinal venous insufficiency; Magnetic resonance venography; Multiple sclerosis; Time-of-flight

Multiple sclerosis (MS) is a common debilitating demyelinating neurodegenerative disorder. Prevalence averages 30 per 100,000 globally but with significant regional variability, with particularly high rates (as high as 176 per 100,000) in Canada, the United States, and Central Europe [1]. Although generally accepted as an inflammatory autoimmune process [2] with evidence of a genetic predisposition [3] and environmental or demographic influence [1], the underlying pathogenesis remains elusive. Although a spatial relationship between MS plaques and venous structures has long been described [2], more recently venous pathology as a potential initiator of the disease process [4,5] has been the topic of great interest and scrutiny. The chronic cerebrospinal venous insufficiency (CCSVI) theory, as proposed by Zamboni et al [5] in 2009, hypothesizes that extracranial venous blockages result in complex hemodynamic flow abnormalities within the intra and extracranial venous system. Specific patterns of venous stenosis and collateral drainage were described on duplex ultrasound and catheter venography (CV). The study [5] reported a definitive finding in all 65 patients with clinically diagnosed MS, universally absent in non-MS patients, a perfect association. Much research has been done subsequently [6], but the results of this original CCSVI study have yet to be reproduced.

This article is part of a 3-arm (subjects with MS, their healthy siblings, and unrelated healthy controls) multicenter prospective study designed to assess the validity of the CCSVI theory through 3 modalities, namely Doppler ultrasound, CV, and magnetic resonance venography (MRV). The

Doppler ultrasound and CV findings were published previously [7]. No significant differences were found in the ultrasound findings between MS cases and study controls, and the ultrasound criteria for CCSVI were neither sensitive nor specific for venous narrowing identified on CV. Furthermore, CCSVI [5], involving multiple venous obstructive patterns in combination, was found to be a rarity (<3% of study cohort) on CV, with no significant difference between MS subjects and controls. Conversely, narrowing of any 1 major extracranial vein by >50% on CV was commonly described in both the MS and control groups, with no significant difference between them. Herein we report the findings of this multicenter study related to the extracranial venous anatomy imaged by MRV.

MRV has the advantage of being noninvasive compared with CV and less operator dependent than ultrasound imaging modalities. MRV also provides a large field of view, enabling visualization of the jugular and azygos veins, as well as potential collateral veins in the anterior and posterior neck. Although unenhanced 2-dimensional (2D) time-of-flight (TOF) acquisitions largely focus on anatomy, enhanced time-resolved acquisitions may have the ability to evaluate flow patterns as well. With all of the above attributes, MRV has the potential to be a screening tool for the specific venous obstructions proposed by the CCSVI theory [5]. However, to date, MRV studies have varied in their findings [8–19], and systematic definitions or consensus criteria for reporting venous narrowing on MRV have yet to be defined.

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