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Chronic cerebrospinal venous insufficiency is unlikely to be a direct trigger of multiple sclerosis

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Abstract
Background: Chronic cerebrospinal venous insufficiency, a vascular pathology affecting the veins draining the central nervous system can accompany multiple sclerosis and is suspected to be involved in its pathogenesis.
Objective: This study was aimed at exploring a potential role for chronic cerebrospinal venous insufficiency in triggering multiple sclerosis. If it were venous abnormalities responsible for neurological pathology, one should expect negative correlation, i.e. more severe vascular lesions in the patients with early onset of multiple sclerosis.
Methods: Localization and degree of venous blockages in 350 multiple sclerosis patients were assessed using catheter venography. Statistical analysis comprised evaluation of the correlations between severity of venous lesions and patients' age at onset of the disease.
Results: We found weak, yet statistically significant positive correlations between patients' age at onset of multiple sclerosis and accumulated and maximal scores of venous lesions. The patients, also those with duration of multiple sclerosis not longer than 5 years, who had their first attack of the disease at younger age, presented with less severe vascular lesions.
Conclusion: Positive correlation suggests that venous lesions are not directly triggering multiple sclerosis. There should be another factor that initiates pathological processes in the central nervous system.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) of as yet undetermined etiology. The initial trigger and molecular mechanisms underlying the pathogenesis of MS, despite major advances in the development of MS therapeutics, still remain enigmatic. For

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the time being the ruling MS paradigm is the autoimmune one, which means that that this disease is caused by autoimmune attack against nervous tissue. However, how such an immune reaction is initiated, remains unclear. Moreover, several findings from human studies, especially regarding neurodegenerative aspect of MS, do not fit into this autoimmune dogma (Chaudhuri and Behan, 2005; Haacke, 2011). Recently a unique vascular pathology comprising stenoses of the veins draining the CNS and altered cerebral venous hemodynamics, the so-called chronic cerebrospinal venous insufficiency (CCSVI), has been described (Zamboni et al., 2009; Zamboni and Galeotti, 2010). Since—according to a number of reports—CCSVI is associated with MS (Zivadinov et al., 2011; Lugli et al., 2012; Simka et al., 2011; Mandato et al., 2012; Petrov et al., 2011; Al-Omari and Al-Bashir, 2012; Bastianello et al., 2011), this coexistence has shed new light on potential causes of MS. It has even been suggested that CCSVI may be responsible for initiation and/or progression of this neurological disease (Simka, 2009; Zamboni et al., 2011). The aim of this retrospective analysis was to study a potential role for CCSVI in triggering MS.

2. Patients

A total of 350 patients with venographically-proven CCSVI (venographic criteria are described in Section 3) and clinically defined MS (198 women and 152 men) were included. Venographically-negative MS patients—there were 11 such individuals (3.0%) in this cohort were excluded from this analysis. The patients were aged 15–70 years, with a median age of 43 years. Patients' EDSS (*Extended Disability Status Scale*) scores ranged from 0.5 to 9, with a median score of 6. Clinical type of MS could be determined in 281 cases: 98 patients (34.9%) presented with relapsing remitting, 105 (37.4%) with secondary progressive and 78 (27.8%) with primary progressive course of MS. Clinical and demographic characteristics of the patients in given in Table 1.

The patients were self-referred and reported an MS diagnosis from their local neurologists. The diagnosis of MS was then confirmed by neurologist in our institution, primarily based on patients' medical records. In most of the cases we did not perform any additional MS-specific diagnostic tests. Duration of MS was calculated from the first symptom of the disease. Patients suffered from MS for 0.5–41 years, with a median duration of the disease of 10 years. Ninety-eight patients suffered from MS not longer than 5 years. The disease began at patient's age of 12–60 years, median: 31 years. Initially the patients were demonstrated vascular abnormalities in the internal jugular and azygous veins using Doppler sonography and/or magnetic resonance venography. The diagnosis of CCSVI was then established using standard catheter venography.

Table 1 Demographic and clinical characteristics of the patients.

Characteristics	Patients	%
Sex		
Female	198	56.6
Male	152	43.5
Race		
White	348	99.4
Other	2	0.6
Clinical type of MS		
Relapsing remitting	98	34.9
Secondary progressive	105	37.4
Primary progressive	78	27.8
Undetermined	69	-
Total	350	100

3. Methods

This survey was a post-hoc analysis of an initial study: open-label clinical trial on endovascular treatments for CCSVI. The entire study has been planned to assess safety and efficacy of endovascular procedures performed to alleviate venous outflow blockages in the main veins draining the CNS in MS patients. The study, including clinical assessment and all necessary preprocedural diagnostic tests (Doppler sonography, MR venography and catheter venography), was approved by the Bioethical Committee of the Regional Silesian Board of Physicians in Katowice, Poland (approval No: 7/2010). It has been registered at ClinicalTrials.gov, identifier: NCT01264848. All patients provided their written consent to undergo the tests and procedures.

Patients' age and duration of the disease were obtained while taking the histories. Catheter venography of extracranial veins draining the CNS: the internal jugular veins, the brachiocephalic veins and the azygous vein, the first part of endovascular procedure, was performed under mild sedation and local anesthesia. Diluted (1:1) iodine-containing contrast, Iodixanolum (Visipaque®, Amersham Health AS, Norway), was used. The following venographic flow patterns, categorized into four grades (Ludyga et al., 2010), were regarded as abnormal:

- grade 1: venous outflow slowed down (i.e., a retention of injected contrast in the examined vein longer that one cardiac cycle), no reflux detected;
- grade 2: venous outflow slowed down, mild reflux and/or pre-stenotic dilation of the vein;
- grade 3: venous outflow slowed down, with reflux and outflow through collaterals and
- grade 4: no outflow through the vein, huge outflow through collaterals.

Severity of vascular pathology was measured in three ways:

- an accumulated score of the venous lesions involved the sum of the grades of venous abnormalities (for example, if the left internal jugular vein was grade 1 and the right internal jugular vein was grade 2, then the accumulated score was 3; all outflow blockages in the left brachiocephalic veins were arbitrary scored as 2 since in this big vein the categorized grading system was difficult to establish);