

Extracranial Jugular Venous Insufficiency in Multiple Sclerosis Patients Treated with Interferon Beta

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Background: The term „vascular immunology” was created when recent studies have suggested that topographic perivenous pattern of demyelinated MS plaques may be caused by venous congestion. This condition termed as „chronic cerebrospinal venous insufficiency” has raised important issues. Our **objective** was to investigate the haemodynamics of the internal jugular vein (IJV) using extracranial Color-Doppler (ECD) sonography in MS patients treated with IFN- β .

Methods: 140 patients with MS (mean age: 41.1 \pm 9.2, mean EDSS: 2.73 \pm 1.96, 68.6 % RRMS and 31.4 % SPMS, mean relapses in the past 12 months: 0.43 \pm 0.61 with at least 18 months of IFN- β treatment as unique DMT, underwent ECD with detection of four parameters: A – reflux present in IJV; B – evidence of proximal IJV stenosis; C – flow not Doppler detectable in IJV; D – negative difference in the cross sectional area in IJV supine/sitting postures. We studied which criteria correlate significantly with EDSS, number of relapses, form of MS and time to initiation of therapy.

Results: Thirty patients (21.8 %) had at least 2 unilateral parameters present on IJV. This patients had significantly more frequent SPMS ($p=0.02$), higher EDSS ($p=0.04$) and started later IFN- β therapy ($p=0.03$). Taken separately, the number of parameters C+D correlates significantly with EDSS ($p=0.04$) and form of MS ($p=0.01$).

Conclusions: ECDS is non-invasive, repeatable, cost-effective and permits to investigate the cerebral venous outflow. The frequency of ECDS criteria in our patient group is significantly lower compared with the results published by Zamboni et al. The absence of IJV flow and negative difference in the cross sectional area in IJV supine/sitting postures correlates significantly with the patient’s clinical characteristics.

Keywords: extracranial jugular venous insufficiency, extracranial color doppler sonography, multiple sclerosis

Introduction

As the etiopathogenesis of multiple sclerosis (MS) remains in debate, the hypothesis of chronic cerebrospinal venous insufficiency (CCSVI) has gained attention in the scientific community. This new theory suggests that MS may develop secondarily to an impaired venous outflow from the central nervous system (CNS). Venous reflux may lead to the accumulation of iron in the CNS, triggering secondary autoimmune events leading to MS [1].

“Perivenular cuffing of lymphocytes, microglia activation and proliferation, axonal damage, and neuronal apoptosis are the major aspects of white matter and gray matter MS pathology but the mechanisms that initiates the autoimmune attack on CNS is still speculative and all hypotheses remain open” [2,3,4].

High-resolution magnetic resonance venography enables to visualize, *in vivo*, the venous architecture and can clearly demonstrate the perivenous location of MS lesions [5].

CCSVI syndrome is determined by obstruction at different levels of the internal jugular vein (IJV), vertebral veins (VV), azygous system and lumbar venous plexus. Zamboni et al. focused their evaluation on 5 anomalous parameters of cerebral venous drainage and defined as abnormal the presence in a single subject of at least 2 of these parameters. Four CCSVI types have been proposed by Zamboni et al. who found an association between CCSVI and MS. They found in as much as 100% of MS patients having CCSVI vs 0% of controls [6]. Professor Zamboni did not claim that these were the etiology of MS but he comments that venous reflux overloads the microcircula-

tion, leading to the activation of matrix metallo-proteinase that in turn digest basement membrane-type IV collagen and fibronectin, allowing migration of cells into the CNS [7]. Other authors have also found sonographic signs of abnormal venous outflow in a majority of MS cases.

Khan et al. discuss the recent investigations that led to the description of CCSI and point out the need to conduct carefully designed and rigorously controlled studies to investigate CCVS [8]. Doepp et al. challenge the hypothesis that cerebral venous congestion plays a significant role in the pathogenesis of MS; this group performed an extended extracranial color-coded Doppler sonography (ECDS) and transcranial color-coded sonography (TCDS) study in both MS patients and controls and no differences were seen [9]. The latest study published failed to detect a significant difference in the Zamboni et al. criteria for impairment to cerebral venous drainage in patients with MS compared with control subjects [10].

Interferon- β (IFN- β) is the major immunomodulatory treatment for relapsing remitting MS (RRMS). However, maximum two thirds of patients with RRMS respond to treatment. Criteria to classify patients into responders and non-responders to IFN- β therapy are usually applied after 1 or 2 years of follow-up, using disability progression or relapse rate [11].

Material and methods

This is a prospective study which included MS patients diagnosed and treated in First Neurological Department of the Emergency County Hospital Tîrgu Mureș. A number of 140 MS patients fulfilling the revised McDonald diag-

nostic criteria, were included in the study between March 2010 and January 2011 [12].

All patients underwent ECDS with detection of four parameters: A – reflux present in IJV; B – evidence of proximal IJV stenosis; C – flow not Doppler detectable in IJV; D – negative difference in the cross sectional area in IJV supine/sitting postures (Δ CSA) [13].

We studied which criteria correlates significantly with EDSS, number of relapses, form of MS and time to initiation of therapy.

The ultrasound examination was performed with a high-resolution color-coded duplex sonography scanner (Siemens Accuson Antares) using a high frequency (5–10 MHz) linear probe for the cervical veins. The examination was performed by an experienced neurosonographer, always in the same room, in a quiet atmosphere, with patients lying first and then in a supine position.

For the ultrasonographical definition of the above mentioned ECDS parameters (reflux in IJV, stenosis; no flow and negative difference in the cross sectional area in IJV supine/sitting postures- Δ CSA) we used the examination techniques and criterias described by Menegatti et al. [14].

Despite Zamboni, we performed only ECDS so we defined as modified CCSVI (mCCSVI) the presence of 2 unilateral parameters.

All patients were neurologically examined 12 months before ECDS testing. In addition, for each patient we collected demographic data, took a medical history, recorded the age, clinical form of MS, the score for neurological deficit EDSS (Expanded Disability Status Score), the change in the EDSS within the last 12 months of treatment, the number of relapses in the last year, the moment of initiation of IFN- β : “early treatment” was considered if the immunomodulatory treatment was initiated within the first year after MS was diagnosed or after the first relapse, while “late treatment” was considered when the patient started IFN- β therapy after at least 18 months of clinically definite MS. The patients were classified according to treatment response in “responders” (no relapse or maximum a rise of 0.5 points on EDSS in the previous year under IFN- β) and “non-responders” (minimum 1 relapse or an increase of at least 1 EDSS point in the last year).

The informed consent of all participating subjects was obtained and the study was approved by the local ethics committee and was carried out according to the Declaration of Helsinki.

Inclusion/exclusion criteria

Eligible patients had multiple sclerosis according to the McDonald criteria. Further inclusion criteria were: age 18–60 years; RRMS and SPMS (secondary progressive MS); minimum 18 months under constant IFN- β treatment (Avonex, Rebif or Betaferon). All patients had negative blood test for other autoimmune or infectious diseases: lupus, antiphospholipid syndrome, HIV infection, syphilis, Lyme disease, etc.

Patients were excluded if they had changed IFN- β preparation within 18 months before ECDS. Also, we did not include any patients with other chronic disease associated to MS, nor those previously treated with immunosuppressive agents. We excluded from the study those subjects having a CNS pathology of a venous nature, including history of venous thrombosis, Behcet disease or other vasculitis.

Statistical analysis

Differences between the groups were described using standard statistics, evaluated for significance using two-sample t-tests or Wilcoxon's rank-sum tests depending on whether the distributional assumptions were satisfied judging by skewness-kurtosis tests.

Correlations between continuous variables were evaluated by calculating Pearson's or Spearman's coefficients depending on whether the linearity assumption was satisfied. Coefficients were estimated complete with 95% confidence intervals (based on Fisher's transformation) and p-values, both for the whole sample and stratified for patient group.

Objectives

The primary objective was to evaluate the haemodynamics of IJV using ECDS sonography in MS patients treated with IFN- β .

The secondary objectives were: a) to find if one of the four ECDS criteria used correlates with the response to IFN- β ; b) determine whether early starting of treatment in newly diagnosed MS patients influences the presence of the modified CCSVI; c) find correlations between modified CCSVI and other patients' MS characteristics (age, sex, clinical form of MS, number of MS relapses, EDSS, change in the EDSS score in the previous year, type of IFN- β administered).

Results

Clinical Data

The mean age of MS patients was 41.1 ± 9.2 years (range 21–59 years); 97 (69.3%) were female, 43 (30.7%) were male (female/male ratio: 2.26/1); EDSS at onset was 2.73 ± 1.96 (range: 0–7.5). Characteristics of all MS patients are displayed in Table 1.

Ultrasound Data, analysis of Doppler Parameters

Overall, we have analyzed 1120 IJV Doppler parameters from which a total of 195 were abnormal.

Two or more abnormal ECDS unilateral findings (mCCSVI) were observed in 30 (21.8%) of 140 MS patients. According to the described criteria, 137 (98%) of the MS patients showed abnormal findings (at least one modified parameter), but only 21.8% of them had mCCSVI.

The frequency of ECDS parameters in MS patients was: 1 – IJV reflux present in 98 (70%) patients; 2 – evidence of proximal IJV stenosis in 37 (26.4%) patients; 3 – IJV flow not Doppler detectable in 45 (32.1%) patients; 4 – nega-

Table 1. Demographics, clinical and therapeutical characteristics of MS patients

Patients characteristics	Value (percentage)
MS age at onset; at testing	36.7±9.4; 41.1± 9.2
Women/men	97 (69.3 %) / 43 (30.7%)
EDSS	2.73±1.96
Number of relapses within previous year	0.43±0.61
RRMS	96 (68.6%)
SPMS	44 (31.4%)
Patients on IFN-β 1b; 1a s.c.; 1a i.m.	92; 37; 11
Patients "early treated"	54 (38.6%)
Patients "late treated"	86 (61.4%)

tive difference in the IJV cross sectional area supine/sitting postures in 15 (10.5%) patients.

We found 153 anomalous parameters on the right IJVs and 132 on the left IJVs. Reflux, stenosis and reverted postural control of the IJV were more frequently found on the right side (87 vs. 60; 39 vs. 33; 6 vs. 3), but no flow detectable in IJVs was more frequently present on the left side (36 vs. 21). This difference was not significant.

Bilateral reflux was found in 45 cases (21.7% of all patients with reflux), bilateral stenosis in 12 cases (30.8% of all patients with stenosis) and bilateral absence of IJV detectable flow in 9 cases (20% of all patients with this flow abnormality). We have never found bilateral reverted postural control of the IJVs.

Reflux and reverted postural control in the IJVs were more frequent in females (66% vs. 58%; 10.9% vs. 9.8%), while the other two parameters were more frequently anomalous in males: stenosis (47% vs. 36%) and no flow detectable (41% vs. 27%).

Regarding the age of the patients, reflux and stenosis of IJV were found more often at the age group 20–40 years comparing with patients older than 40 years, while no IJV flow detectable and reverted postural control were more often seen at the group aged >40 years.

In patients with SP form of MS, reflux in the IJV was more frequently found and this group included all patients

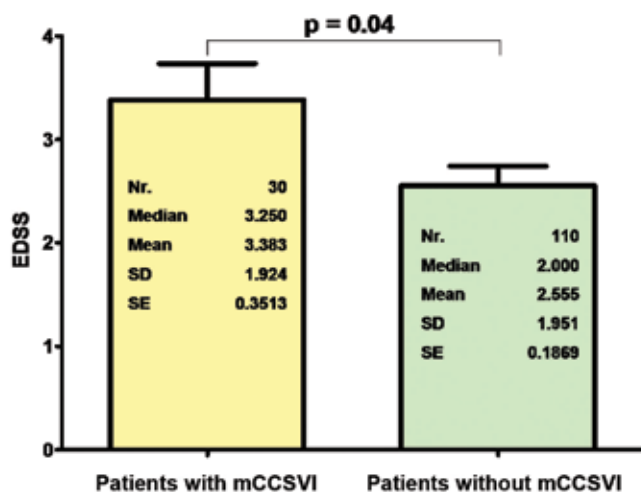


Fig. 1. EDSS in patient groups with and without mCCSVI

where we found a negative Δ CSA of the IJV. Patients with a RR evolution of MS had stenosis and lack of detectable flow in IJV in a higher proportion than those with SPMS.

The mean disease duration was the highest in patients having reverted postural control with $p < 0.001$, extremely significant in comparison with the mean disease duration of the rest of patients.

We find no significant correlation between the number of the four ECDS parameters (1+2+3+4) and patients' clinical data. If we calculated separately the criteria 1+2 and 3+4, we found a significant correlation between the latter (3+4) (flow not detectable and negative Δ CSA) and the EDSS of the patients ($p=0.04$). No other correlations were statistical significant.

Dividing the patients into two groups: with mCCSVI and no mCCSVI, we did not find any significant differences regarding: gender, age distribution, clinical MS course, type of onset, mean disease duration. In contrast, the presence of mCCSVI is statistically significantly ($p=0.04$) associated with a higher EDSS (3.38 vs. 2.55) (Figure 1).

Another very important significant association ($p=0.05$) was the number of high number of recurrences in patients with mCCSVI comparing with the rest of cases (2.3 vs. 0.34).

Patients with mCCSVI had a significantly ($p=0.03$) longer time from MS onset to initiation of disease modifying therapies (DMT) than those with no CCSVI (8.26 vs. 5.11) (Figure 2.)

Discussion

We studied the possible causative association between modified CCSVI and MS.

We haven't used TCDS because in some patients the transtemporal bone window is difficult to find, this examination is time consuming, the deep cerebral veins are difficult to insonate, an optimal equipment is necessary and some misinterpretations of the blood flow might appear.

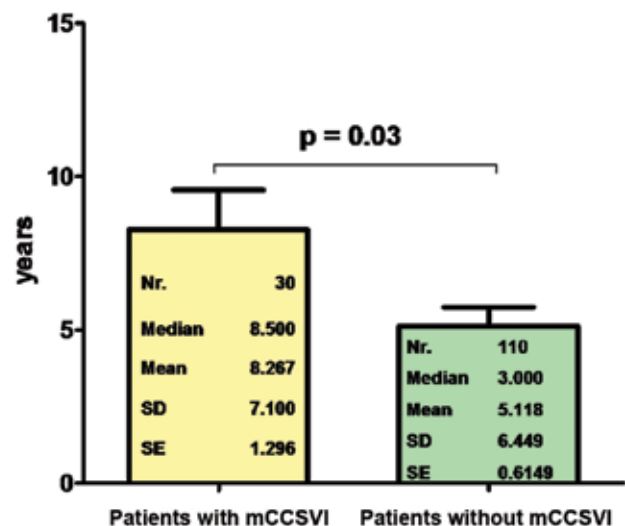


Fig. 2. Time between the first MS symptoms and initiation of disease modifying treatment (years).

With regards of ECDS, false-positive results might be noted due to the pulsation artifact from the adjacent carotid artery and the physiologic backflow which is present only in the first segment of the IJV, if a Valsalva maneuver (which is a more adequate method to test venous reflux) is not used, a reflux due to IJV valve incompetence can be misinterpreted for a reflux due to IJV stenosis. Also a compression of IJV by the transducer or by neck muscles, anatomic and physiologic variations of IJV diameter could lead to false-positive stenoses [15].

In our study 98% of the MS patients showed abnormal findings (at least one modified Doppler parameter), value close to the results reported by Al-Omari and Rousan in their study, where 92% of 25 MS patients showed abnormal findings. Both values are higher than the percentage found by Baracchini et al. in his study where ECDS was abnormal only in 52% of the 50 MS patients evaluated [2,16]. This difference might be explained by distinct types of equipment, the lack in our study of TCDS examination (the fifth Zamboni's CCSVI parameter) and overall the arguments regarding the ECDS artifacts presented above.

The main parameter that interested us, mCCSVI was present in 21.8% of our cases. Literature data is very inconsistent regarding the presence and frequency of CCSVI: a) it has been found by Zamboni et al. in 84–100% of MS cases and never in controls [13], Al-Omari and Rousan found CCSVI in 84% of cases [16], and Simka in 90% [17]; b) Zivadinov et al., in a large cohort of 500 patients including 280 MS cases, found CCSVI in 56% in Ms and 23% in control patients [18]; c) Baracchini et al. found CCSVI in 16% of 50 MS cases [15]; d) Doepp et al. studied 56 MS cases and 20 healthy subjects but did not find clear evidence of CCSVI [9]. The following factors might account for discrepancies in the results obtained in different CCSVI evaluations: methodological aspects (ultrasound technique, some of the mentioned studies used in addition other imagistic methods like MRI venography, cerebral angiography with venous time), occasional consideration of thoracic veins like Azygos, differences between patient groups, chance, bias from various sources, design flaws, lack of objectivity.

We could not find an epidemiological pattern in patients with mCCSVI. The major statistical significant differences were in the course of the disease: a) higher EDSS ($p=0.04$); b) higher number of relapses ($p=0.05$); c) longer time from MS onset to DMT initiation ($p=0.03$). Zamboni et al. noticed in their study that Doppler abnormalities indicating CCSVI were more pronounced in patients with higher disability score [13].

Our study has several limitations: ECDS gave us the only date regarding the IJV venous circulation (lack of other radiological techniques), the ECDS was performed once and by a single investigator, thus not permitting the assessment of the intraobserver and interobserver variability. However we do not think the above limitations significantly compromise the validity of our findings.

Sundstrom et al. performed contrast-enhanced magnetic resonance imaging (MRI) on MS patients vs. healthy subjects and found no differences regarding IJV outflow, or the presence of IJV blood reflux. They assume that a decreased cerebral venous outflow in MS may be secondary to a decreased arterial inflow. MRI perfusion studies in MS show significantly decreased cerebral blood flow (CBF). Moreover, decreased CBF has been associated with brain atrophy, which is common in MS patients [1].

Baracchini et al. enrolled 35 patients with SPMS, 25 patients with PPMS and 60 age- and gender-matched normal controls into a cross-sectional CCSVI study. Their findings indicate that CCSVI is not a late secondary phenomenon of MS and is not associated with disability. Their results question the existence of CCSVI [15].

A lot of personalities of the medical society found no support for a treatment rationale of endovascular procedures like angioplasty or stenting.

Additional mechanisms have been considered to explain cerebral hypoperfusion in MS: 1) a diffuse astrocyte dysfunction, possibly related to an abnormal release of K^+ in the perivascular space and a reduced degree of vasodilatation; 2) mitochondrial injury, secondary to toxic inflammatory mediators, reactive oxygen, nitric oxide species. Moreover, given the tight coupling between arterial flow, tissue metabolism and venous flow, the reduced intracranial venous volume and structural changes in extracranial veins draining the CNS in patients with MS may represent an adaptive physiologic response to low intracranial vascular-arterial input and low brain metabolism. Given the elasticity and collapsibility of veins, in some patients with MS, narrowing and stenosis may occur as a result of the disease process, and is very probable that opening these collapsed veins would not be in the benefit of patients [19,20]. This concomitant disturbance of the brain microcirculation deserves further investigation, but can be well explained by secondary vascular inflammatory changes known to occur in MS.

The contra- reactions to Zamboni's theory are: a) Increased cerebral venous pressure occurs in central venous thrombosis, idiopathic intracranial hypertension, yet none of these is associated with MS [8]; b) transient global amnesia is well known to occur in association with jugular venous insufficiency, but is not a feature of MS [21]; c) radical neck dissection is a procedure in the management of head and neck cancer which removes all jugular veins, but MS never was a complication of such surgery [9]; d) the wall of IJV is very thin and thus can easily be compressed either manually or by surrounding anatomical structures [15]; e) the nearby carotid artery may cause pulsation artifact [15].

Zamboni has promoted balloon dilatation to treat outflow problems "liberation treatment". The results of the treatment can be watched on YouTube, as thus far, no trial data are available, no randomized controlled trials are in progress. The basis for this new treatment rests on anecdote-

tal evidence, in addition the procedure showed complications, as published by Reekers et al. [22].

A study of ECDS and TCDS performed in the ongoing study conducted by Zivadinov has shown that the narrowing of extracranial veins is, at very least, an important association in MS but the suggested treatment – endovascular procedures – can not be considered useful. There are also uncertainties about the appropriate imaging investigations to diagnose CCSVI, the vascular and anatomic properties that define CCSVI, the indications for angioplasty and/or stenting and the safety, effectiveness and durability of these procedures. These treatments are experimental at this time [18].

Conclusions

ECDS is non-invasive, repeatable, cost-effective and permits to investigate the cerebral venous outflow.

A percentage of 21.8% of MS patients showed evidence of mCCSVI. The frequency of ECDS criteria in our patient group was significantly lower compared with the results published by Zamboni et al. Patients with mCCSVI had a significantly higher EDSS, than those without IVJ flow impairment. Patients with mCCSVI had significantly longer time from MS onset to initiation of DMT. The criteria 3+4 was more frequently found in patients with higher EDSS. CCSVI is poorly reproducible, requires training, experience and a good sonographic machine

Perhaps it is time to start thinking of a "vascular immunology" in the study of neurological disease and to keep on asking if MS has a vascular component.

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