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Original article

Morphological and haemodynamic abnormalities in the jugular veins of patients with multiple sclerosis

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Abstract

***Objectives*:** Multiple areas of stenosis and different levels of obstruction of internal jugular and azygous veins (a condition known as cronic cerebrospinal venous insufficiency) recently emerged as an additional theory to the well-known autoimmune concept, explaining etiology of multiple sclerosis (MS). The aim of our study was to evaluate internal jugular vein (IJV) morphology and haemodynamic characteristics in patients with MS and compare it with well-matched healthy individuals and to evaluate the prevalence of venous flow abnormalities in both groups.

***Methods*:** Sixty-four patients with clinically proven MS and 37 healthy individuals were included in our study. In all patients, IJV morphology and haemodynamic characteristics were evaluated by colour Doppler sonography as well as venous flow disorder. The patients were classified into four groups according to MS clinical form presentation. The prevalence of morphological and haemodynamic abnormalities in the IJV were assessed.

***Results*:** The presence of stenosing lesion, mostly intraluminal defects like abnormal IJV valves, were observed in 28 patients (43%) in the MS group, and in 17 patients (45.9%) in the control group ($P = \text{NS}$). By adding haemodynamic Doppler information in the IJV venous outflow was significantly different in 42% of MS patients showing flow abnormalities (27/64), as compared with 8.1% of the controls (3/37), $P < 0.001$.

***Conclusion*:** In our group of patients, patients suffering from MS had significantly more IJV morphological changes and haemodynamic abnormalities when compared with healthy individuals not suffering from MS. These findings can be well demonstrated by non-invasive and cost-effective Doppler ultrasound.

Keywords: chronic cerebrospinal venous insufficiency; multiple sclerosis; internal jugular vein

Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory and degenerative disease of the central nervous system (CNS).[1] Focal demyelination of white matter is considered to be a pathognomonic lesion for MS diagnosis.[2]

The relationship between cerebral veins and focal lesions in patients with MS has been described based on a hypothesis of blood-brain barrier (BBB) disruption in the course of an autoimmune reaction.[3,4] As an addition to autoimmune theory, in recent years vascular theory emerged, claiming that demyelinating MS lesions might be a result of chronically impaired venous drainage from the brain.[5,6]

A condition known as chronic cerebrospinal venous insufficiency (CCSVI)[5,6] is characterized by multiple areas of stenosis and different levels of obstruction of internal jugular veins (IJV) and azygous veins resulting in a collateral venous drainage formation.[7,8] These findings led to a new vascular MS model.

According to this theory, venous obstruction induced venous flow anomalies in the brain and in the neck, which consequently resulted in

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increased concentration of adhesion molecules on the BBB, iron deposition, inflammation and BBB function attenuation.[9] This process initiates inflammation and neurodegeneration causing the neurological deficits that characterizes MS.

Different venous abnormalities can be found in patients with CCSVI: stenosis, complete occlusion, distortions, intraluminal structures such as membranes, webs and inverted valves.[6,8]

CCSVI extracerebral venous morphology and haemodynamics characteristics can be easily assessed in patients with MS by colour Doppler sonography with changes in posture.[6] The aim of our study was to assess the haemodynamic and morphology characteristics of the jugular veins using colour Doppler sonography in patients with MS and compare it with subjects showing no signs of MS.

Methods

Sixty-four patients with clinically proven MS according to the McDonald criteria[10] were included in our study as well as 37 healthy individuals. The examination was performed with the patients in the sitting and supine positions. We investigated the morphology of the IJVs by means of high-resolution B-mode ultrasounds and haemodynamics according to the presence of reflux and/or absence of flow, as previously descibed (Figures 1 and 2). For IJVs morphological and haemodynamic abnormalities assessment we used following parameters: (1) IJV stenosis (D1, D2 and D3 segments) – segmental one or both IJV vein stenosis when IJV diameter is 2.5 mm during the Valsalva manoeuvre; (2) IJV confluence stenosis with prestenotic dilation (spontaneous diameter >15 mm) and decreased

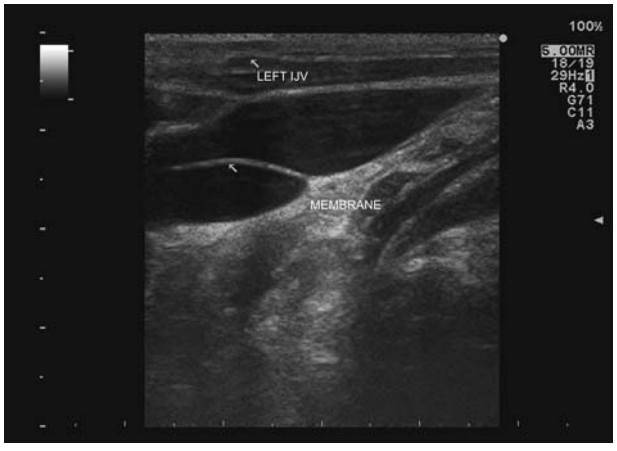

Figure 1 (Left) Colour Doppler sonography: membrane presence at the level of the left IJV valve causing turbulent flow with BFV (blood flow velocity) > 130 cm/second

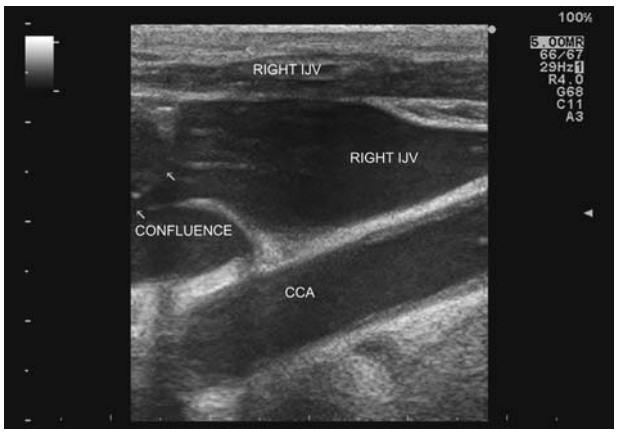

Figure 2 (Right) Colour Doppler sonography: abnormal – fibrosed valve at the right IJV confluence

prestenotic flow (<20 cm/second) if increased in-site stenotic flow was >130 cm/second; (3) abnormal IJV valves: inverted, fibrous modified valve or the presence of membranes in the area of valve; (4) IJV reflux – significant when persistent for more than 0.88 seconds; (5) negative changes in cross-sectional area (CSA) of IJV were measured in both sitting and supine position and (6) other parameters regarding IJV haemodynamic characteristics: IJV occlusion, reverse IJV flow or IJV hypoplasia. In addition to abnormal venous outflow parameters for IJV assessment described earlier[7], we used two more parameters (parameters 1 and 2) that on the basis of haemodynamic disorders indicated significant morphological IJV changes.

According to the course of MS the patients in the first group were classified into four subgroups: (1) benign form; (2) relapsing remitting form – unpredictable attacks followed by slow remission (symptoms and signs improvement); (3) secondary progressive form – progressive form with initially relapsing remitting course and (4) primary progressive (PP) form – with gradually worsening symptoms.

The frequency of morphological abnormalities and haemodynamic parameters of the IJVs were compared between the patients with MS and healthy controls as well as among the patients with MS only, according to the clinical form of the disease and the disability level.

The study was approved by the ethical committee of our institution and all patients gave their consent for ultrasonographic examination.

Results

Demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1 Demographic characteristics and MS form distribution in the MS group compared with group without MS

Form of the disease	BF ($n = 9$)	RR ($n = 37$)	SP ($n = 11$)	PP ($n = 7$)	Patients with MS (total) ($n = 64$)	Control group ($n = 37$)
Male (patients)	6	16	6	3	31	17
Female (patients)	3	21	5	4	33	20
P	1 ($P > 0.05$)	0.675 ($P > 0.05$)	0.091 ($P > 0.05$)	0.143% ($P > 0.05$)	0.063 ($P > 0.05$)	0.243 ($P > 0.05$)
Mean age, (year; SD)	32.33 (4.5)	36.42 (7.9)	44 (9.4)	34 (5.2)	37.26 (7.8)	39.33 (4.5)
EDSS score (SD)	2 (1–2.5)	4 (1–6.5)	5 (2–6.5)	6 (5.5–6.5)	4.4 (1–6.5)	0
Mean disease duration (year; SD)	2 (1–5)	9 (3–21)	10 (5–21)	7 (5–9)	9.33 (1–21)	0

MS, multiple sclerosis; BF, benign form; RR, relapsing remitting form; SP, secondary progressive form; PP, primary progressive form; EDSS, Expanded Disability Status Scale

A total of 64 patients (31 men, 33 women) with confirmed diagnoses of MS were assesed as well as 37 healthy individuals (17 men, 20 women) in the control group ($P > 0.05$). In the MS group, nine patients had benign MS form, 37 relapsing remitting form, 11 patients had secondary progressive MS form while seven patients had primary progressive disease form.

Median patient age was 37.3 years (28–53 years) for the MS group and 39.3 years (35–43 years) for the control group. Median duration of the disease in the MS group was 9.3 years, ranging from 1 to 21 years.

In the MS group, all patients were evaluated for Expanded Disability Status Scale (EDSS) score which ranged from 1 to 6.5 with an average EDSS score of 4.4.

Intraluminal defects, like abnormal IJV valves, were observed in 28 patients (43%) in the MS group, and in 17 patients (45.9%) in the control group ($P = \text{NS}$).

When patients with MS were observed, IJV confluence stenosis (Figure 3) was seen in 25 patients (39%), the majority in relapsing remitting form (17 patients, 26.5%) and negative changes in CSA in 12 patients (18%). Persistent reflux in the IJV (Figure 4) was seen in 23 patients (35.9%), the majority also in relapsing remitting form (15 patients, 23.4%). IJV occlusion, reverse IJV flow or IJV hypoplasia were seen in only two patients (3.1%), both in relapsing remitting form, while IJV stenosis was seen in four patients (6.2%).

When IJV abnormalities parameters were observed on the basis of the clinical form of the disease, IJV confluence stenosis (17/64 patients, 26.5%) and abnormal IJV valves (17 patients, 26.5%) were the most frequent parameters verified in relapsing remitting form. Similary, in benign and secondary progressive form, abnormal IJV valves were the most common parameters verified

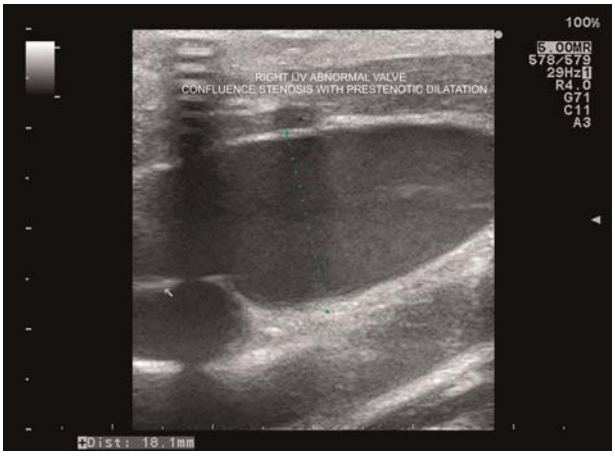

Figure 3 Colour Doppler sonography: right IJVconfluence stenosis with prestenotic dilation – spontaneus diameter >15 mm with decreased blood flow velocity (BFV, < 20 cm/second) and increased in-site stenotic BFV >130 cm/second

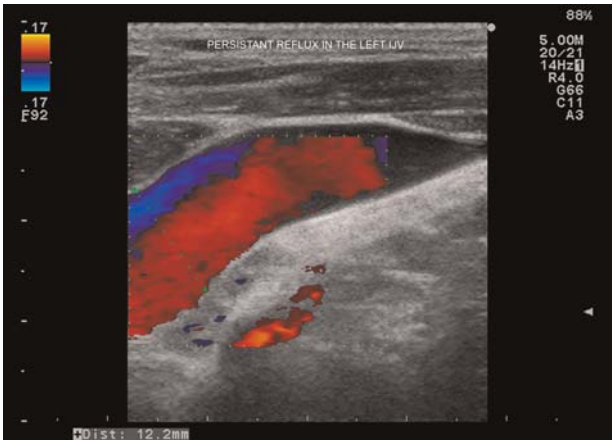

Figure 4 Colour Doppler sonography: persistent reflux in the left IJV – persistent for more than 0.88 seconds

(33.33% for benign form and 63.6% for secondary progressive form).

Statistically significant difference was verified within all MS group forms when parameters'

frequent occurence was observed ($P < 0.01$), except for IJV stenosis and other parameters regarding IJV haemodynamic characteristics ($P = \text{NS}$).

As seen in the MS group, the most common parameter present in the control group was abnormal IJV valves (17 patients, 45.9%); IJV confluence stenosis was seen in eight patients (21.6%) as well as IJV persistant reflux. No changes in the CSA of the IJV were registered in seven patients (18.9%) and none of the patients had IJV stenosis or other parameters regarding IJV haemodynamics.

Although no statistically significant differences in the frequency of stenosing lesion was observed between patients with MS and healthy controls, adding haemodynamic Doppler information in the IJV venous outflow was significantly different in 42% of MS patients showing flow abnormalities (27/64), as compared with 8.1% of the controls (3/37), $P < 0.001$.

Discussion

A condition called CCSVI described by Zamboni *et al.*, which is characterized by multiple changes in extracranial venous drainage pathways, showed strong correlation with MS.[5–8] This resulted in an additional model of MS etiology, together with a widely accepted autoimmune model, in which the immune system is sensitized to myelin by external influences.

Zamboni *et al.*[6] described four different patterns of pathological venous outflow associated with MS: type A – obstruction of the proximal azygous vein accompanied by stenosis of one IJV; type B – bilateral IJV stenosis and proximal azygous vein obstruction; type C – normal azygous vein and bilateral IJV stenosis and type D – azygous vein system multiple stenoses and occlusions.

All these might result in IJV haemodynamics changes that could be assessed by non-invasive and cost-effective colour duplex sonography.[6] The main finding of this study was to demonstrate a significantly higher prevalence of morphological and Doppler haemodynamics abnormalities in patients with MS in relation to healthy subjects.

Our study showed that 42% of the patients with MS had Doppler haemodynamic evidence of venous flow abnormalities as compared with 8.1% of the healthy controls. These data not only indicate that venous flow abnormalities were significantly associated with the presence of MS but also indicate that it can be seen in the population not suffering from MS, yet the difference remains statistically significant ($P < 0.001$).

Initial studies have shown the correlation of CCSVI and MS with nearly 100% specificity and sensitivity.[5,6] Zamboni *et al.*[6] have published results of their study in which 100% of the patients with MS (109/109 patients) had two or more positive CCSVI criteria. The most common criterion was reflux in the IJV and/or vertebral veins which was seen in 69.7% of the patients (76/109 patients). Confirming this thesis, Simka *et al.*[11] showed that 90% of the patients with MS (63/70) had two or more positive CCSVI criteria, while 91.4% of the patients (64/70) had at least one positive criterion.

In contrast to this, Doepp *et al.*[12] published their results in which none of the 56 patients with MS fulfilled more than one Zamboni criterion. They concluded that the cerebral venous drainage in patients with MS is not restricted and have challenged the hypothesis that venous congestion plays a significant role in the pathogenesis of MS.

In a similar way, Khan *et al.*[13] have challenged the CCSVI theory proposed by Zamboni *et al.*,[5,6] and strongly opposed endovascular procedures that utilize stenting, before such studies have been completed, analysed and debated in the scientific arena.

Researchers at Buffalo University[14] attempted to replicate Zamboni's study, using the same Doppler technology and measuring the same five blood flow parameters to determine CCSVI presence in 1600 subjects (950 clinically defined MS patients, 100 initial demyelinating events, 300 other CNS diseases and 350 healthy controls). They released the results of phase 1 of their study (280 MS patients, 161 healthy controls) and found that CCSVI was verified in 56% of the patients with MS, 22% in healthy controls and 80% in those with advanced MS.

They concluded that CCSVI is definitely associated with MS and that CCSVI must be a part of the MS disease process. An interesting finding was that the higher the disability the higher is the chance of CCSVI being involved, suggesting that if one had MS and CCSVI, there was a much higher chance of disease progressing to a higher disability level than in a person with MS but no CCSVI.

The limitation of our study is that we did not examine the CCSVI prevalence in patients with MS because we did not investigate the intracranial and vertebral veins. The aim of our study was to evaluate morphological and haemodynamic IJV abnormalities in patients with MS and compare it with healthy controls. For morphological and haemodynamic abnormalities assessment of the IJVs, we used some of Zamboni's criteria and two other parameters (parameters 1 and 2), which in our practice proved to be a good indicator of IJV flow disorder.

Although the results of our study do not show a significant difference in the presence of stenosing lesions between patients with MS and healthy controls, by adding haemodynamic Doppler information in the IJV flow abnormalities were significantly more present in MS patients as compared with controls ($P < 0.001$).

Conclusion

In our group of patients, MS was significantly associated with IJV morphological changes and haemodynamics when compared with healthy individuals not suffering from MS. These findings can be well demonstrated by non-invasive and cost-effective Doppler ultrasound. Future studies are needed to explain a definite correlation between CCSVI and MS, and thus elucidate the place of endovascular procedures as an appropriate treatment for this severe disease.

Acknowledgements

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