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Endovascular Treatment for Chronic Cerebrospinal Venous Insufficiency in Patients with Multiple Sclerosis

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ABSTRACT: Objective. The aim of this study was to evaluate the impact of endovascular treatment for chronic cerebrospinal venous insufficiency on chronic fatigue in multiple sclerosis patients. **Methods.** Severity of fatigue was measured with Fatigue Severity Scale (FSS) in 340 patients before the treatment and after 6-month follow-up. **Results.** We found statistically significant improvement of fatigue. After the treatment, mean FSS score dropped from 4.7 to 3.8. However, these post-procedural changes were not evenly distributed. While the patients with no fatigue (FSS<2.0) or mild/moderate fatigue (FSS 2.0-3.9) did not report significantly changed fatigue, the patients with severe fatigue (FSS≥4.0) experienced a statistically significant drop of FSS scores, which in this subgroup was 1.21. Such variables as the patients' gender, age, duration of the disease, or localization of vascular lesions did not influence the level of postprocedural improvement of fatigue. **Conclusion.** Our results confirm the findings of the previous studies that have found a positive effect of endovascular treatment on chronic fatigue in multiple sclerosis patients. Despite all limitations of our study, improved fatigue, especially when severe, appears to be an encouraging finding, which warrants further study in this area.

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Key words: endovascular therapy, neurovascular interventions, quality of life

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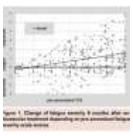
Chronic fatigue (CF) is one of the most common and the most troubling manifestations of multiple sclerosis (MS), the chronic and debilitating disease of the central nervous system.[1,2] MS is believed to be an autoimmune disorder, which means that disease is caused by autoimmune attack against nervous tissue antigens.[3] Efficacy of pharmacological and other treatments for MS is primarily evaluated in terms of such objective parameters as the plaque load or relapse rate, while the quality-of-life impairments related to this disease are poorly addressed by mainstream research. The new idea that MS may be related to stenoses in the veins draining the brain and spinal cord, the so-called chronic cerebrospinal venous insufficiency (CCSVI),[4] and that alleviation of these vascular blockages may improve patients' clinical status and their quality-of-life, is currently hotly debated by the scientific community. In this paper we present the results of an open-label study on clinical impact of endovascular procedures for CCSVI in the patients with associated MS, with focus at fatigue improvement after such a treatment.

Patients and methods

This open-label study was aimed at the assessment of safety and clinical efficacy of endovascular procedures in CCSVI patients with associated MS. Quality-of-life changes following venous angioplasties were measured with: Multiple Sclerosis Impact Scale-29, Fatigue Severity Scale (FSS), Epworth sleepiness and heat intolerance questionnaires.



This report focuses at fatigue improvement after endovascular treatment for CCSVI. There were assessed 340 patients, 191 women and 149 men, with clinically defined MS. The diagnosis of MS was given according to the revised McDonald criteria[5] and this diagnosis, if determined elsewhere, was confirmed by the consulting neurologist at our institution. The patients were aged 15-68 years, with a median age of 42 years. They suffered from MS for 0.5 to 47 years, with a median duration of the disease of 9 years. In all these patients catheter venography of extracranial veins draining the central nervous system (the internal jugular veins and the azygous vein) was performed, followed by angioplasty of narrowed veins in a case of detection of vascular pathology. The following venographic flow patterns were regarded abnormal and, if technically feasible, warranting angioplasty:

- No outflow through the vein;
- Venous outflow slowed down (*ie*, a retention of injected contrast in the examined vein longer that one cardiac cycle);
- Reversed flow direction (reflux);
- Outflow through collaterals;
- Intraluminal structures (webs, septa, or membranes), hypoplasia or narrowing of the vein compromising outflow (ie, incurring the retention of injected contrast, reflux, or collateral outflow);
- Pre-stenotic dilation of the vein associated with slowed down flow or reflux;
- Complete occlusion or agenesis of the vein.

Importantly, venous valves in the junction of the internal jugular vein (IJV) with brachiocephalic vein were recognized as pathologic only if such a valve compromised the outflow. Prevalence of venous outflow abnormalities in MS patients, which can be found as high as 96.1%, was debated in our recent paper,[6] while the details of venographic protocols, as well as of endovascular treatment of malformed veins, are described in the other article.[7] The most frequent abnormality found was the stenotic valve of the IJV. Such stenotic valves were typically seen in combination with collapsed middle and upper parts of this vein. Still, usually this collapse actually resulted from an awry hemodynamic and was no longer seen after successful angioplasty of such an over-competent valve. Other vascular lesions, for example stenoses not related to the valves, were rarely encountered. Consequently, in most of the cases, treatment comprised endovascular valvuloplasty (forced dilatation or disruption of fused valve leaflets and/or restricting annulus) with the use of angioplastic balloons. Functional narrowing of the veins was not managed routinely. Only in some cases when such a narrowing in the middle segment of the jugular vein was seen in combination with stenotic valve, we implanted a self-expandable stent covering the valve and narrowed venous segment.

After the endovascular procedure the patients stayed in the hospital overnight and were discharged the next day (on condition that no serious complication occurred). Patients were instructed to continue their standard (immunomodulating and symptomatic) medication for MS.

Severity of CF syndrome was evaluated by means of FSS questionnaire.[8,9] Fatigue assessment was done before the treatment and 6 months after endovascular procedure. Fatigue was defined as severe (FSS≥4.0) or mild/moderate (FSS 2.0-3.9). Patients with FSS scores 1.0-1.9 were defined as not exhibiting CF.

In addition to the above-described patients who underwent endovascular treatments, we analyzed retrospectively those MS patients in whom catheter venography was negative (ie, no venous abnormalities were found). Records on fatigue severity were available from 38 such patients: 26 women and 12 men, aged 18-63 years, with a median age of 37 years.

Statistical analysis

The Wilcoxon signed rank sum test and the one-way ANOVA tests were used to verify the null hypothesis that endovascular treatment had no influence on post-procedural level of fatigue, against the alternative hypothesis that the treatment resulted in improvement of this MS symptom. The tests were considered significant at $P<0.05$. The one-way ANOVA test was also used to compare fatigue severity and fatigue changes over the patients' subgroups (age, sex, duration of the disease, localization of venous lesions). Differences between the subgroups were considered significant at $P<0.05$.

Results

Distribution of chronic cerebrospinal venous insufficiency and safety issues

Outflow blockages were found in one vein draining the central nervous system in 139 patients (40.9%), in 2 veins in 196 cases (57.6%), and in 3 veins in 5 cases (1.5%). The majority of the lesions were treated using balloon angioplasty, while the stents were implanted only if no flow improvement was obtained after standard angioplasty. Distribution of venous lesions is presented in Table 1. Most of the procedures were uneventful. In this group of patients only a few, non-life threatening complications occurred: post-procedural thrombosis of subclavian vein (resolved after standard treatment with low-molecular-weight heparin) in 1 case; early thrombotic occlusion of implanted stent (resolved after repeated angioplasty and low-molecular-weight heparin administration) in 1 case; local bleeding from the groin (including one pseudoaneurysm) in 2 cases; minor gastrointestinal bleeding, probably evoked by clopidogrel in 1 case; and difficulty removing angioplastic balloons in 3 cases.

MS-associated chronic fatigue

Pre-procedural FSS scores varied from 1 to 7 points, with mean score of 4.7 points and median score of 4.9 points. Two hundred forty-one patients (70.9%) presented with severe fatigue (FSS≥4.0), 67 patients (19.7%) with mild/moderate fatigue (FSS 2.0-3.9), and 32 patients (9.4%) with no fatigue (FSS<2.0). No statistically significant differences ($P>0.05$) were found between the patients' pre-procedural fatigue in terms of their age, sex, and duration of the disease. MS patients without venous lesions presented with the same severity of fatigue as CCSVI-positive patients: mean FSS 4.7 and median FSS 4.9.

Six months after the treatment, mean FSS dropped from 4.7 to 3.8 points and median FSS from 4.9 to 3.8 points. Mean and median FSS changes were: minus 0.89 and minus 0.70, respectively. This decrease in fatigue level was statistically significant ($P<0.00001$, both in the Wilcoxon and one-way ANOVA tests). One hundred-forty-five patients (42.6%) reported at least 1.0 point decrease in the FSS (fatigue improvement), 28 patients (8.2%) reported at least 1.0 point increase (fatigue worsening), while FSS scores of the remaining 167 patients (49.1%) remained largely unchanged (change less than ±1.0 point). However, those post-procedural changes of fatigue were not evenly distributed. While the patients with no fatigue (FSS<2.0) and mild/moderate fatigue (FSS 2.0-3.9) reported no significant post-procedural changes ($P>0.05$ in the Wilcoxon and one-way ANOVA tests), MS patients with severe fatigue (FSS≥4.0) experienced statistically significant improvement ($P<0.00001$ in both statistical tests). This difference in fatigue improvement between severely fatigued patients and those with no or mild/moderate fatigue was statistically significant ($P<0.001$). No statistically significant difference in fatigue improvement ($P>0.05$) was demonstrated when the patients were grouped according to their sex, age, duration of the disease, or localization of vascular lesions.

Details regarding fatigue levels in the patients' subgroups are given in Table 2.

Discussion

Fatigue is a very common symptom of MS. It affects over 80% of these patients and 30% of them find fatigue as the most disabling manifestation of the disease.[1,2,10] MS-related fatigue is very different from a normal fatigue. It comprises a subjective lack of physical and mental energy, or a state of exhaustion not caused by depressed mood and physical weakness. Prevalence of CF among MS patients is higher in males, older patients, those diagnosed at an older age, unemployed, less educated, and exhibiting higher level of disability. Although a positive correlation between CF and extended disability status scale (the scale most frequently used for the assessment of MS-related disability) has been demonstrated in some studies, there are also papers that did not report such a link.[1]

MS-associated fatigue remains an underinvestigated and undertreated aspect of this disease. An effective treatment for severe fatigue in MS patients is not currently available. Although there are some drugs that are used for its symptomatic management such as amantadine, modafinil, pemoline, and 4-aminopyridine[1,11-13] their clinical efficacy is limited.[14,15] Moreover, the pathomechanism responsible for this unique type of fatigue remains elusive.

In this open-label study we demonstrated an improved fatigue in MS patients 6 months after endovascular treatment for obstructive lesions of the veins draining the central nervous system. This improvement, measured with the FSS questionnaire, was primarily seen in the patients with severe fatigue, while less fatigued patients did not report significant changes of this symptom. Such parameters as patient's age, sex, duration of the disease, or localization of venous lesions were not associated with different likelihood of improved fatigue after the treatment.

It should be emphasized that there are some limitations of our study. Our study was open-label without a control group. The results should be interpreted with caution. CF can be measured with different questionnaires. The FSS, a 9-item scale, is the most often used. This scale can be applied to monitor changes in fatigue over time or in response to therapeutic interventions. The FSS is based on patients' responses to each statement on a scale of 1 to 7, with 1 indicating strongly disagree and 7 indicating strongly agree. The sum of responses was then divided by 9 and a higher score indicates higher fatigue level. The FSS usually defines severe fatigue as a score of at least 4.0 across the 9 questions and mild/moderate fatigue as average score less than 4.0. Still, the FSS, similarly to all self-reported scales, exhibits some restrictions. It asks a patient to assess the fatigue without clearly defining such a fatigue, it is subjective, and susceptible to a placebo effect.[16] Despite these limitations, FSS remains the most commonly used measure of fatigue severity in MS patients. In addition to the subjectivity of the FSS, in this report we were not assessing the technical success of the endovascular procedure at the time of follow-up (*ie*, if the veins treated remained fully open or, on the contrary, a restenosis developed). Since a restenosis can be accompanied by worsening of MS symptoms,[17] it is possible that our rate of success in terms of fatigue improvement was underestimated and could be improved after additional endovascular procedure addressing such a problem. Taking into account a slowly progressing natural course of MS, the 6-months follow-up seems to be a rather short period.

Proponents of a venous paradigm of MS suggest that CF associated with this disease may simply be a reflection of chronic ischemia of the brain resulting from impaired venous outflow from this organ.[18] Indeed, several radiological studies that have used magnetic resonance techniques, have demonstrated a hypoperfusion of cerebral tissue that was equivalent to a mild cerebral stroke,[19-23] while a reduced glucose metabolism in white matter adjacent to prefrontal cortex, premotor cortex, and basal ganglia in severely fatigued MS patients has been revealed by the study that has used positron emission tomography imaging technique.[24] These phenomena were poorly understandable within the autoimmune model of MS. Interestingly, the recent study on pO_2 and pCO_2 in blood samples obtained from IJVs before and after angioplasty revealed a dramatic improvement of these blood gas parameters, indicating a better oxygenation of the brain after the endovascular procedure *(Petrov I. Results of endovascular treatment of CCSVI in patients with multiple sclerosis; presented at 14th Annual Meeting of the Australasian College of Phlebology; March 30-April 3, 2011, Melbourne, Australia)*. However, our finding that CCSVI and non-CCSVI multiple sclerosis patients presented with the same fatigue scores, casts doubt on the idea that MS-associated fatigue is simply caused by an impaired venous outflow from the brain. On the other hand, it is not easy to explain an improved CF primarily in severely fatigued patients. One may argue for a placebo effect responsible for this fatigue improvement, but such an effect should not be selective. Obviously, all these uncertainties should be solved by well-designed randomized controlled trials and our study may provide a useful framework for future research.

Current therapeutic strategies for MS predominantly target a hypothetically awry immune response. Unfortunately, these treatments, even if successful in some domains, do not address all pathological aspects of MS, especially quality-of-life impairments, including CF. The venous model of MS is not necessarily contrary to its currently ruling autoimmune paradigm. The autoimmune and venous manifestations may actually represent two sides of the same coin, with MS being a disease triggered and exacerbated by both immune and vascular mechanisms. Our results confirm the findings of the previous studies that have demonstrated a positive effect of endovascular treatments on CF in MS patients.[25-27] Despite all limitations of our study, improved fatigue, especially in the patients suffering from severe onset, seems to be an encouraging finding, warranting further studies in this area.

The entire study protocol, including pre-procedural imaging diagnostics, catheter venography, endovascular treatments for detected vascular pathologies and neurological assessment of the patients was approved by the Bioethical Committee of the Regional Silesian Board of Physicians in Katowice, Poland (approval No: 7/2010). All patients provided their written consent to undergo these procedures and tests. The study has been registered at ClinicalTrials.gov, identifier: NCT01264848.

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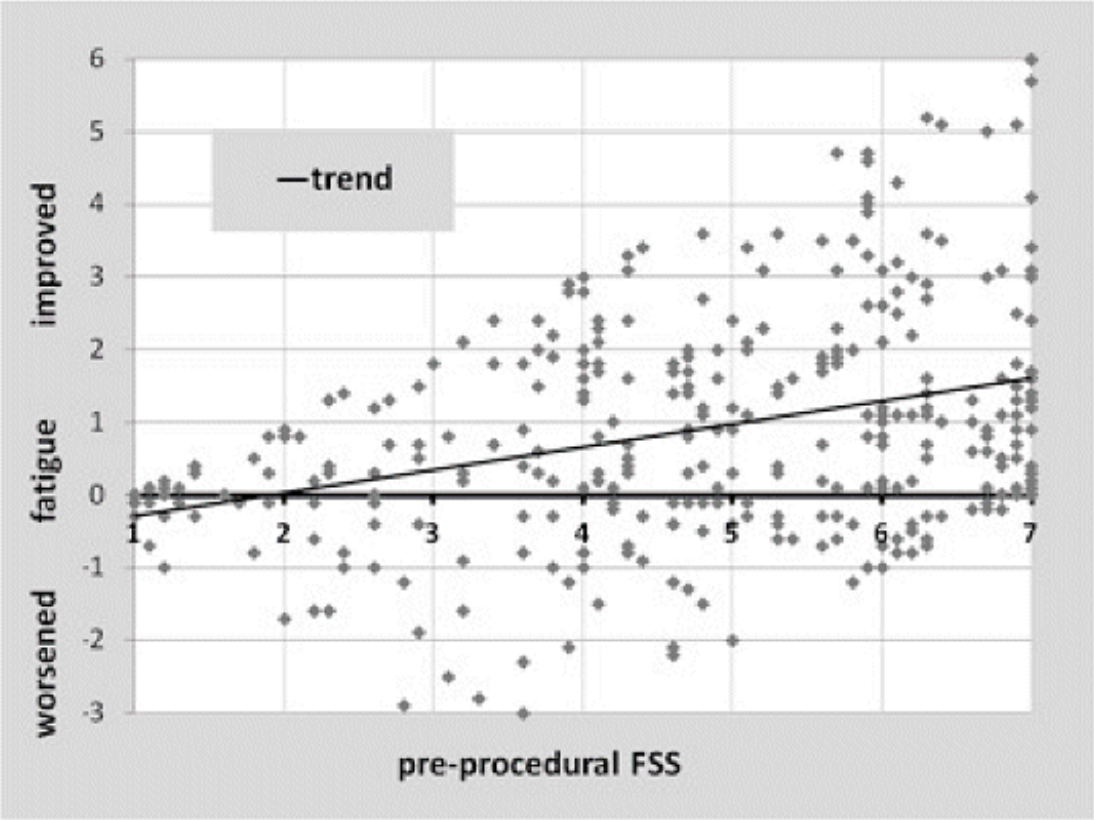

Figure 1. Change of fatigue severity 6 months after endovascular treatment depending on pre-procedural fatigue severity scale scores.

Table 1. Distribution of venous lesions.

Venous lesion	Number of patients	Percentage
Left internal jugular vein	100	29.4%
Right internal jugular vein	38	11.2%
Both internal jugular veins	190	55.9%
Azygos vein	1	0.3%
Left internal jugular vein + azygos vein	5	1.5%
Right internal jugular vein + azygos vein	1	0.3%
Both internal jugular veins + azygos vein	5	1.5%

Table 2. Pre- and post-procedural fatigue.

	Mean FSS before treatment	Mean FSS change	At least 1.0 point decrease in FSS	FSS change less than ±1.0 point	At least 1.0 point increase in FSS
All patients	4.7	-0.89	42.6%	49.2%	8.2%
Patients with pre-procedural severe fatigue (≥4.0)	5.6	-1.21	52.3%	43.1%	4.6%
Patients with pre-procedural mild/ moderate fatigue (2.0-3.9)	3.0	-0.18	28.4%	42.3%	23.9%
Patients without pre-procedural fatigue (<2.0)	1.3	+0.02	0	96.9%	3.1%
Patients aged <40 years	4.3	-0.86	44.8%	46.8%	8.4%
Patients aged ≥40 years	5.0	-0.89	40.5%	50.3%	9.2%
Patients history <10 years	4.5	-0.89	42.3%	49.6%	8.1%
Patients history ≥10 years	4.9	-0.90	43.0%	47.1%	9.9%
Patients with pathological left internal jugular vein only	4.4	-0.86	41.0%	48.0%	11.0%
Patients with pathological right internal jugular vein only	5.0	-1.03	42.1%	50.0%	7.9%
Patients with pathological both internal jugular veins (azygos vein normal)	4.8	-0.85	43.2%	48.9%	7.9%
Patients with pathological azygos vein	5.0	-1.25	50.0%	41.7%	8.3%
Male patients	4.7	-0.73	43.5%	49.2%	7.3%
Female patients	4.7	-1.01	41.6%	47.7%	10.7%

FSS = fatigue severity scale