Report

Background report on whether treating MS/CCSVI by cerebrospinal vein dilatation complies with established medical science and medical practice

ICD-10 code: G35 Multiple sclerosis

Multiple sclerosis (of):
. NOS
· brain stem
· cord
· disseminated
· generalized

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Publication	College voor zorgverzekeringen (CVZ) (dutch national health insurance board) P.O. Box 320 1110 AH Diemen Fax (020) 797 85 00 E-mail info@cvz.nl Internet www.cvz.nl
Case number	2011028062
Series number	2011067042
Department	ZORG-ZA
Authors	A. Veerman, MD; H.M. Gaasbeek Janzen, PHMD
Direct line	Tel. +31 (0) 20 797 88 64

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Summary

The basis for using venous angioplasty as a treatment for multiple sclerosis (MS), is the presumed pathophysiological mechanism of chronic cerebrospinal venous insufficiency (CCSVI). The concept of CCSVI, whether or not the presumed cause of MS, has not been generally accepted.
No evidence has been found for the efficacy of angioplasty as a treatment for MS. Using venous angioplasty to treat MS (with presumed CCSVI) does not comply with established medical science and medical practice.

1. Introduction

1.a. Reason

A dispute has arisen between a health insurer and an insured client with multiple sclerosis as to whether the client has a right to angioplasty (percutaneous balloon dilatation, "Dottering") of the draining veins of the brain and spinal cord. The insured client is said to have had "cerebrospinal venous insufficiency" (CCSVI). In order to be eligible for (the reimbursement of) this treatment at the expense of the basic insurance, the use of angioplasty for MS/CCSVI must comply with the established medical science and medical practice criterion. This background report goes into this in more detail.

1.b. Background of multiple sclerosis

Concepts

Multiple sclerosis (MS): a chronic disease of the central nervous system, see the following paragraphs for a description.
Dottering, angioplasty, balloon dilatation (with or without stent placement): a technique for treating strictures of the arteries/veins by means of intravenous catheters.
Venous insufficiency: insufficient drainage of blood via arteries.
Cerebrospinal veins: vena jugularis and vena azygos.

(Patho)physiology

The cause of MS is unknown. A great deal is known about the pathophysiology. The phenomena associated with MS are caused by inflammatory lesions (of a non-infectious nature), that can occur in all sorts of places in the white matter of the brain and spinal cord of MS patients. The symptoms and complaints at any given moment are determined by the location of the inflammatory lesions, the degree to which the lesions are active and the degree to which they have caused permanent damage.

Spontaneous course

The first symptoms of MS usually begin between twenty and forty years of age. Depending on the location of the inflammatory lesions, these could be disorders relating to eyesight, speech, eye movements, coordination of the limbs, spastic paralysis, sensation or urinary incontinence. The phenomena usually occur periodically, with a tendency to become more severe and to leave behind more severe phenomena after each period of disease (relapse, exacerbations). In the long term, the course is often chronic, progressive, ending with severe damage to the locomotor system and often severe multiple invalidity. Its course differs enormously between individuals and is unpredictable. There are also cases in which the course is benign and patients reach old age with relatively few limitations[1].

Prevalence

The prevalence of MS varies throughout the various regions of the world. Its prevalence varies from 1-30 per 100,000 in equatorial regions, to more than 100 per 100,000 in Scotland and the surrounding groups of islands. Numbers varying between 30 to 100 per 100,000 have been reported in north-western Europe. MS is found about twice as often in women as in men. The statistics can vary, depending on the chosen diagnostic criteria[1,2].

Standard Treatment/Comparative treatment

There are no known medicines or methods that can cure MS. There are products that can have a favourable effect on its course. Some medicines have been proven to influence the course of the disease in MS patients. These medicines work by affecting the immunological system. For example, corticosteroids are used for relapses, and beta-interferons, glatiramer acetate and possibly natalizumab are currently used to reduce the number of relapses[3].

Hypothesis behind the new intervention

Zamboni developed the theory[4] that the inflammatory lesions in MS are due to venous stasis. The idea was the result of a presumed similarity between MS lesions and iron-dependent inflammations such as those seen in venous stasis in the legs. His later research[5] is supposed to have demonstrated a strong relationship between clinically established MS and venous draining via the vena jugularis and the vena azygos. These veins transport blood from the brain and the spinal cord respectively. He referred to this state as: chronic cerebrospinal venous insufficiency (CCSVI). Up until that moment, the concept CCSVI had not been used as a diagnostic category.

Hypothesis disputed

The concept CCSVI, which Zamboni specifically introduced as possible cause of MS, has not received universal recognition as a diagnostic or pathophysiological category. Zamboni's findings and the possible therapeutic consequences have raised a great deal of discussion. It is within this framework that the research of Wattjes et al.[6] failed to find a single correlation between MS and the existence of venous defects. Ghezzi[10] et al. also failed to find any points of departure for a relationship between the quality of cerebrospinal veins and MS. There were large variations in the course of the disease and in vein thickness, both in the MS patients and in the controls. On the other hand, a study is currently taking place with 1000 test subjects (CTEVD-study in Buffalo). An interim analysis of the first 500 subjects by Zivadinov et al.[7] revealed statistics consistent with an increased prevalence of venous hemodynamic limitations in the cerebrospinal veins. The results for the entire group have not yet been published.

New intervention, Subject of this report	The CCSVI hypothesis has led some doctors to treat MS with interventions on the veins involved, the purpose of which is to relieve the stasis, presumed or otherwise: angioplasty. This can be done by means of balloon dilatation (also known as 'Dottering'), whereby a stent may or may not be left behind in order to keep the blood vessel open. The question is, therefore, whether in actual practice there is evidence that angioplasty has been of benefit in cases of MS. Since the essence of the matter is not the validity of the concept of CCSVI, but the efficacy of venous angioplasty in cases of MS, henceforth the term is only used in the sense of 'presumed CCSVI'.

1.c. Question to be answered by the literature study

Question	Does venous angioplasty fulfil the established medical science and medical practice criterion as a form of treatment for MS (with presumed CCSVI)?
Patient population	Patients suffering from any form of MS.
Relevant outcome indicators	All clinical outcome indicators that reflect the severity of the neurological symptoms and/or the frequency and duration of remissions and exacerbations.
Relevant follow-up duration	The natural course of MS varies enormously per individual and is unpredictable and spread out over many years. This means that a proper conclusion about the efficacy or lack of efficacy of treatment can only be drawn after a follow-up that lasts several years and involves proper monitoring of the clinical picture.
Required methodological study characteristics	For the same reasons that make a long follow-up necessary, in order to reach a proper conclusion, is it essential to choose a good randomised comparative study set-up, in a sufficiently large study population, based on a power analysis.

2. Search strategy & selection of suitable studies

Search terms	In April 2011 CVZ carried out a literature search looking for publications reporting on the effects of angioplasty of the cerebrospinal veins on the course of MS. The search was carried out in Medline (PubMed), using the algorithm: (MS OR multiple sclerosis) AND (CCSVI OR Chronic cerebrospinal venous insufficiency). This led to a selection of articles relating to treatment with angioplasty (appendix 1).
Databases & websites	The literature search involved Medline, EMBASE, without any time restrictions. The search was also carried out in the Trial Register.
Selection criteria	Selection from the literature found took place based on abstracts. If articles could not be excluded on the basis of the abstract, the whole article was examined.
Inclusion and exclusion criteria	The only articles considered were those that provided facts and figures on effects on the course of MS. Studies that focussed on different outcome indicators, such as, for example, safety and implementability, were not considered because they would only be relevant to this report if there were indications of favourable effects on the course of MS. Anything less than comparative research was not considered sufficient. In particular because this is a disease with widely diverging symptoms and an unpredictable and variable course.

3. Results

3.a. Results of the literature search

The literature search did not reveal a single article for inclusion. Two studies by Zamboni et al. [8] [9] were excluded. Though these did report a form of clinical outcome indicators, such as QoL and MS phenomena, or the lack of a relapse, there was no comparative element whatsoever. It is impossible to say whether the outcomes reveal the natural course of the disease, or revealed non-specific effects or results of selection bias.

Not a single comparative study was found that reported facts and figures on the course of MS after treatment with angioplasty.

The trial register found four current trials into the effects of angioplasty on MS (see in appendix 1: studies 1 to 4). The proposed end dates of the studies are between 2010 and 2015. These results are not yet available.

3.b. Standpoints and guidelines

No standpoints or guidelines were found in which a role was played by the concept CCSVI or the treatment of MS with angioplasty. These concepts did not appear in the draft guidelines on MS recently published by the CBO.[3]

4. Discussion

There are wide variations in the development and size of cerebrospinal veins found in both MS patients and in controls[10]. Studies into a correlation between venous strictures and MS contradict one another[6]. The concept CCSVI has not been generally accepted. Treatment on this basis, i.e., angioplasty on MS patients, with or without presumed CCSVI, has not resulted in any proper evaluations in the peer-reviewed literature.

5. Consultation regarding contents

The Dutch Association for Neurology sent the draft of this report to the chairman of the MS guideline work-group, the neurologist mr. L.H. Visser, MD PhD, asking him to send any comments to CVZ.
He commented that the report provides a good overview of the current state of affairs in relation to venous angioplasty in cases of MS. He fully endorses the conclusion of the report. The references to the recent CBO draft guidelines were incorporated in response to his suggestion[3]. He also pointed out the recently published interim results of the CTEVD study in Buffalo[7].

6. Standpoint regarding established medical science and medical practice

There is no scientific evidence for the efficacy of widening the cerebrospinal veins of MS patients.
The treatment of MS (with presumed CCSVI) using venous angioplasty does not comply with established medical science and medical practice.

7. Literature list

[1] Minderhoud JM, et al. Mutiple sclerosis. 2nd Dr. Houten: Bohn Stafleu Van Loghem, 1999.
[2] Adams RD, Victor M, Ropper AH. Principles of Neurology 6th ed. New York: McGraw-Hill, 1997: 905-8.
[3] CBO. Draft Guidelines for Diagnostics, Treatment and Functioning in Multiple Sclerosis. Utrecht, 2011.
[4] Zamboni P. The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. J R Soc Med 2006; 99: 589-93.
[5] Zamboni P and Galeotti R. The chronic cerebrospinal venous insufficiency syndrome. Phlebology 2010; 25: 269-79.
[6] Wattjes MP, van Oosten BW, de Graaf WL, et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow quantification study. J Neurol Neurosurg Psychiatry 2011; 82: 429-35.
[7] Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology 2011 Apr 13 [Epub ahead of print]
[8] Zamboni P and Galeotti R. The chronic cerebrospinal venous insufficiency syndrome. Phlebology 2010; 25: 269-79.
[9] Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009; 50: 1348-58.
[10] Ghezzi A, Comi G, Federico A. Chronic cerebrospinal venous insufficiency (CCVSI) and multiple sclerosis. Neurol Sci 2011; 32: 17-21.

Appendix 1: literature search

Treatment of CCSVI in patients with multiple sclerosis
Search date: 14-04-2011
Case no. 2011028062

Medline (PubMed)

(MS[tiab] OR multiple sclerosis)
AND
(CCSVI[tiab] OR Chronic cerebrospinal venous insufficiency)

Selection of articles (therapy)

Clinical trial

1. Ludyga T, Kazibudzki M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010; 25: 286-95.
Abstract: OBJECTIVES: The aim of this report is to assess the safety of endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI). Although balloon angioplasty and stenting seem to be safe procedures, there are currently no data on the treatment of a large group of patients with this vascular pathology. METHODS: A total of 564 endovascular procedures (balloon angioplasty or, if this procedure failed, stenting) were performed during 344 interventions in 331 CCSVI patients with associated multiple sclerosis . RESULTS: Balloon angioplasty alone was performed in 192 cases (55.8%), whereas the stenting of at least one vein was required in the remaining 152 cases (44.2%). There were no major complications (severe bleeding, venous thrombosis, stent migration or injury to the nerves) related to the procedure, except for thrombotic occlusion of the stent in two cases (1.2% of stenting procedures) and surgical opening of femoral vein to remove angioplastic balloon in one case (0.3% of procedures). Minor complications included occasional technical problems (2.4% of procedures): difficulty removing the angioplastic balloon or problems with proper placement of stent, and other medical events (2.1% of procedures): local bleeding from the groin, minor gastrointestinal bleeding or cardiac arrhythmia. CONCLUSIONS: The procedures appeared to be safe and well tolerated by the patients, regardless of the actual impact of the endovascular treatments for venous pathology on the clinical course of multiple sclerosis, which warrants long-term follow-up
Pub. type: Clinical Trial
Journal Article
ISSN: 1758-1125

Review

1. Zamboni P and Galeotti R. The chronic cerebrospinal venous insufficiency syndrome. Phlebology 2010; 25: 269-79.
Abstract: Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenosies of the internal jugular and/or azygous veins (IJVs-AZ) with opening of collaterals and insufficient drainage proved by reduced

cerebral blood flow and increased mean transit time in cerebral MRI perfusional study. The present review is aimed to give a comprehensive overview of the actual status of the art of the diagnosis and treatment of this condition. As far as the origin of venous narrowing is concerned, phlebographic studies of the IJVs and AZ systems demonstrated that venous stenoses were likely to be truncular venous malformations; mostly, they are intraluminal defects such as malformed valve, septa webs. CCSVI condition has been found to be strongly associated with multiple sclerosis (MS), a disabling neurodegenerative and demyelinating disease considered autoimmune in nature. In several epidemiological observations performed at different latitudes on patients with different genetic backgrounds, the prevalence of CCSVI in MS ranges from 56% to 100%. To the contrary, by using venous MR and/or different Doppler protocols, CCSVI was not detected with the same prevalence. Two pilot studies demonstrated the safety and feasibility in Day Surgery of the endovascular treatment of CCSVI by means of balloon angioplasty (PTA). It determines a significant reduction of postoperative venous pressure. Restenosis rate was found out elevated in the IJVs, but negligible in the AZ. However, PTA seems to positively influence clinical and QoL parameters of the associated MS and warrants further randomized control trials
Pub. type: Journal Article
Review
ISSN: 1758-1125

Overige studies

1. Reekers JA, Lee MJ, Belli AM, et al. Cardiovascular and Interventional Radiological Society of Europe commentary on the treatment of chronic cerebrospinal venous insufficiency. Cardiovasc Intervent Radiol 2011; 34: 1-2.
Abstract: Chronic cerebrospinal venous insufficiency (CCSVI) is a putative new theory that has been suggested by some to have a direct causative relation with the symptomatology associated with multiple sclerosis (MS) [1]. The core foundation of this theory is that there is abnormal venous drainage from the brain due to outflow obstruction in the draining jugular vein and/or azygos veins. This abnormal venous drainage, which is characterised by special ultrasound criteria, called the "venous hemodynamic insufficiency severity score" (VHISS), is said to cause intracerebral flow disturbance or outflow problems that lead to periventricular deposits [2]. In the CCSVI theory, these deposits have a great similarity to the iron deposits seen around the veins in the legs in patients with chronic deep vein thrombosis. Zamboni, who first described this new theory, has promoted balloon dilatation to treat the outflow problems, thereby curing CCSVI and by the same token alleviating MS complaints. However, this theory does not fit into the existing bulk of scientific data concerning the pathophysiology of MS. In contrast, there is increasing worldwide acceptance of CCSVI and the associated balloon dilatation treatment, even though there is no supporting scientific evidence. Furthermore, most of the information we have comes from one source only. The treatment is called "liberation treatment," and the results of the treatment can be watched on YouTube. There are well-documented testimonies by MS patients who have gained improvement in their personal quality of life (QOL) after treatment. However, there are no data available from patients who underwent unsuccessful treatments with which to obtain a more balanced view. The current forum for the reporting of success in treating CCSVI and thus MS seems to be the Internet. At the CIRCE office and the MS Centre in

Amsterdam, we receive approximately 10 to 20 inquiries a month about this treatment. In addition, many interventional radiologists, who are directly approached by MS patients, contact the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) for advice. Worldwide, several centres are actively promoting and performing balloon dilatation, with or without stenting, for CCSVI. **Thus far, no trial data are available, and there is currently no randomized controlled trial (RCT) in progress. Therefore, the basis for this new treatment rests on anecdotal evidence and successful testimonies by patients on the Internet.** CIRSE believes that this is not a sound basis on which to offer a new treatment, which could have possible procedure-related complications, to an often desperate patient population
Pub. type: Journal Article
ISSN: 1432-086X

2. Vedantham S, Benenati JF, Kundu S, et al. Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010; 21: 1335-7.
Pub. type: Editorial
Practice Guideline
Research Support, N.I.H., Extramural
ISSN: 1535-7732

3. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009; 50: 1348-58.
Abstract: OBJECTIVE: Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by combined stenoses of the principal pathways of extracranial venous drainage, including the internal jugular veins (IJVs) and the azygous (AZY) vein, with development of collateral circles and insufficient drainage shown by increased mean transit time in cerebral magnetic resonance (MR) perfusion studies. CCSVI is strongly associated with multiple sclerosis (MS). This study evaluated the safety of CCSVI endovascular treatment and its influence on the clinical outcome of the associated MS. METHODS: Sixty-five consecutive patients with CCSVI, subdivided by MS clinical course into 35 with relapsing remitting (RR), 20 with secondary progressive (SP), and 10 with primary progressive (PP) MS, underwent percutaneous transluminal angioplasty (PTA). Mean follow-up was 18 months. Vascular outcome measures were postoperative complications, venous pressure, and patency rate. Neurologic outcome measures were cognitive and motor function assessment, rate of MS relapse, rate of MR active positive-enhanced gadolinium MS lesions (Gad+), and quality of life (QOL) MS questionnaire. RESULTS: Outpatient endovascular treatment of CCSVI was feasible, with a minor and negligible complication rate. Postoperative venous pressure was significantly lower in the IJVs and AZY ($P < .001$). The risk of restenosis was higher in the IJVs compared with the AZY (patency rate: IJV, 53%; AZY, 96%; odds ratio, 16; 95% confidence interval, 3.5-72.5; $P < .0001$). CCSVI endovascular treatment significantly improved MS clinical outcome measures, especially in the RR group: the rate of relapse-free patients changed from 27% to 50% postoperatively ($P < .001$) and of MR Gad+ lesions from 50% to 12% ($P < .0001$). The Multiple Sclerosis Functional Composite at 1 year improved significantly in RR patients ($P < .008$) but not in PP or SP. Physical QOL improved significantly in RR ($P < .01$) and in PP patients ($P < .03$), with a positive trend in SP ($P < .08$). Mental QOL showed significant improvement in RR ($P < .003$) and in PP ($P < .01$), but not in SP. CONCLUSIONS: PTA of venous

strictures in patients with CCSVI is safe, and especially in patients with RR, the clinical course positively influenced clinical and QOL parameters of the associated MS compared with the preoperative assessment. Restenosis rates are elevated in the IJVs but very promising in the AZY, suggesting the need to improve endovascular techniques in the former. The results of this pilot study warrant a subsequent randomized control study
Pub. type: Journal Article
ISSN: 1097-6809

Richtlijn (in voorbereiding)

NICE. Balloon angioplasty with or without stenting for chronic cerebrospinal venous insufficiency (CCSVI) in MS. Verwacht zomer 2011. Informatie beschikbaar via **http://guidance.nice.org.uk/IP/891**.

Google Scholar

Dorne H, Zaidat O, Fiorella D. Chronic cerebrospinal venous insufficiency and the doubtful promise of an endovascular treatment for multiple sclerosis. J NeuroIntervent Surg 2010;2:309-1. [Editorial]
Recently, a radically different concept regarding the pathogenesis of multiple sclerosis (MS) has been proposed. Termed chronic cerebrospinal venous insufficiency (CCSVI), it suggests that macro occlusive abnormalities of the extracranial venous drainage pathways of the brain and spinal cord can cause or contribute to MS. As a consequence of this theory, it has been suggested that angioplasty and possibly stenting of the internal jugular and/or azygos veins can improve the signs and symptoms of MS. These interventions have been performed sporadically across the globe in an open label fashion and never in the context of a well designed, controlled, randomized and blinded clinical trial. Despite this, the procedure has been labeled by some as 'liberation procedure' and caused a firestorm of interest in the medical and MS communities, both for and against its utilization. The arguments on all sides are passionate, ranging from the belief that venous intervention is a miracle cure that must not be withheld from patients, to the feeling that the procedure is ineffective and unwarranted at best and dangerous at worst. The various camps commonly protest that those with differing views are not acting in the best interest of their patients.
As neurointerventionalists interested in interventional treatment of neurological disorders, it is time to take a thorough and objective look at CCSVI. This commentary will examine the origin of the CCSVI theory and discuss the data supporting and refuting its existence. An attempt will be made to critically analyze the available data and provide constructive recommendations about whether or not endovascular therapy represents a reasonable option at this point in time for patients with MS.

Conference abstracts

1. Hall M, Fischbach T, Duprat G. Ultrasound and venographic correlation and the clinical response to balloon angioplasty in CCSVI. J Vasc Interv Radiol 2011; 22: S50.

Abstract: Purpose: Central cerebrospinal venous insufficiency (CCSVI) has recently been proposed as a contributing factor in the pathophysiology of multiple sclerosis (MS). The primary goal of this prospective single center study is to correlate ultrasound and venographic fingings in patients evaluated for CCSVI. Secondary objectives of this study include the safety of balloon angioplasty in the treatment of CCSVI and the short-term clinical outcome. Materials and Methods: This study was IRB approved. 30 patients were enrolled in this single-center prospective study. All patients underwent comprehensive ultrasound evaluation and venography. All patients undergoing angioplasty were assessed with ultrasound postoperatively. Short-term follow-up was obtained at 3-5 months. Patients were assessed for treatment complication and clinical outcome (frequency and severity of MS attacks pre-and post-operatively). Results: 27 of the 30 patients demonstrated abnormal ultrasound findings. All but one of these patients with positive US findings also had positive findings at venography. 2 of the 3 patients with negative ultrasound findings had positive venographic findings. 28 patients were treated with balloon angioplasty. Technical success was acheived in all patients. There were no minor or major complications. Clinical outcomes are currently being reviewed. Conclusion: There was found to be a strong correlation between ultrasound and venographic findings in this prospecitvely evaluated group. There were 2 false negative findings at ultrasound and one false positive. Balloon angioplasty was safe and technically successful for all treated patients. Post-operative clinical evaluations are still in process
ISSN: 1051-0443

2. Haskal Z and Quish A. Feasibility evaluation of catheter-directed interventions in multiple sclerosis CCSVI patients. J Vasc Interv Radiol 2011; 22: S155.
Abstract: Purpose: To report the feasibility results of balloon angioplasty and stent placement for treatment of multiple sclerosis related CCSVI symptoms. Materials and Methods: 18 consecutive patients (5M, 13F), mean age 48 yrs (r, 35-64) with relapsing remitting (n= 10), secondary progressive (n=5), post-progressive (n=1), primary progressive (n=2), unknown (n=1) underwent 19 single-operator procedures. Standardized intervention protocol included IVUS, left and right internal jugular (LIJV, RIJV), azygous venograms in 3-head positions, imaging intensifier angulations, quiet breathing, no sedation. 3-month follow-up; clopidogrel for stents, ASA for PTA. Results: There were 18/19 RIJV and 19/19 LIJV valvular flow restrictions were treated with 10-16mm PTA (most common 14mm RIJV, 12mm LIJV). Mid RIJV (n=2), LIJV (n=5); high LIJV (n=2); and azygous arch stenoses (13/19) with 6-8 mm PTA. 10 tapered and non tapered nitinol stents in 9/19 cases: n=2 azygous, LIJV (n=5, 2mid, 1 upper, 2 valve/lower), RIJV (3 mid/lower overlap). IVUS improved confirmation of MRV stenoses in all cases. % valve stenoses could not be quantified due to dynamic function. Patient self-reported outcomes by interview and MS-QOL: uniformly positive, heterogeneous change except index case. Examples: improved motor function (eg stair climb, foot drop, ability to drive, abandoned of assistive devices, swallowing, breathing effort); sensory (eg resolved/reduced numbness in extremities, better balance); fatigue (reduction), cognitive (reduced/nearly vanished impairment), visual (clarity and color); temperature sensitivity (coldness and heat tolerance). Direct physician clinic observation confirms self-reported motor and balance change. Complications included 1 resolved allergy to clopidogrel; 1 contained LIJV valve rupture, resolved with balloon tamponade, and bare stent.

Conclusion: Catheter directed interventions in MS CCSVI patients can be safely accomplished. Feasibility results confirm strong positive early self reported improvements, some confirmed by direct observation. Conventional thresholds for intervention are not initially predictive, suggesting new scales will need development
ISSN: 1051-0443

3. Mandato K, Johnson JF, Siskin G, et al. The incidence of May-Thurner syndrome in patients with multiple sclerosis (MS) undergoing endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI). J Vasc Interv Radiol 2011; 22: S18.
Abstract: Purpose: To determine the incidence of May-Thurner syndrome (MTS) in patients with MS undergoing pelvic venography prior to endovascular treatment of CCSVI. Materials and Methods: A retrospective analysis of MS patients undergoing pelvic venography during an evaluation for CCSVI was performed. Medical records were reviewed to determine if symptoms classically attributed to MTS were present. Pelvic venograms were reviewed to diagnose MTS; findings were graded based upon the degree of left common iliac vein compression and the presence of pelvic collateral veins (Table 1). Grade 2 and Grade 3 findings were considered positive for MTS. These findings were compared with historical controls. Results: 160 patients (mean age 47 years; range 25-68 years) were included in this retrospective analysis. 66% (105/160) of these patients were female and 34% (55/160) were male. Based on the pelvic venography findings, 17% of patients were found to have MTS (Grade 2 or Grade 3 findings on venography). 74.1% (20/27) of these patients were female, but this difference was not significant (p = 0.378). None of the patients with MTS had a history of deep venous thrombosis (DVT) or left lower extremity swelling. (Table presented) Conclusion: In patients with MS undergoing pelvic venography as part of a CCSVI evaluation, there was a 17% incidence of May-Thurner syndrome. Historically, there is a reported incidence of MTS in 6.3-24% of an asymptomatic population [1,2]. This data therefore suggests that MS patients do not have an increased incidence of MTS. Given these findings, and the fluoroscopic exposure time and contrast dose required to evaluate the pelvic vasculature for MTS as part of a CCSVI venogram, we do not support the routine performance of pelvic venography during these procedures, unless the patient has a history of DVT or leg swelling
ISSN: 1051-0443

4. Mandato K, Hegener P, Siskin G, et al. Safety of outpatient endovascular treatment of the internal jugular and azygos veins for chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis: A retrospective analysis. J Vasc Interv Radiol 2011; 22: S4.
Abstract: Purpose: To evaluate the safety of outpatient endovascular treatment of the internal jugular and azygos veins in MS patients with CCSVI. Material and Methods: A retrospective analysis of MS patients with CCSVI undergoing endovascular treatment of the internal jugular and/or azygos veins was performed to identify and describe the adverse events occurring within 30 days. Results: Over 7 months, 247 procedures were performed in 231 patients. The mean patient age was 48.2 years (range: 25.7-70.2 years); 63.7% were female and 36.3% were male. 49.0% (121/247) of the procedures were performed in a hospital and 51.0% (126/247) were performed in the office setting. 92.7% (229/247) were primary procedures while 7.3% (18/247) were secondary due to restenosis. For patients treated primarily, 86.5% (198/229) underwent angioplasty and 11.4% (26/229) underwent stent placement of at least one vessel; the remaining 5 patients were not treated. For patients treated due to restenosis, 50% (9/18) underwent angioplasty and 50% (9/18)

underwent stent placement. After 99.2% (245/247) of the procedures, patients were discharged within 3 hours. A post-procedure, transient headache was reported in 8.5% (21/247); this persisted beyond 30 days in 1 patient. Neck pain was reported in 15.8% of patients (39/247); 53.8% (21/39) of these patients underwent stent placement. 1.7% (4/231) of patients were retreated within 30 days due to symptomatic restenosis. Sustained cardiac arrhythmias were observed in 3 patients during the procedure with 2/3 patients requiring hospital admission. One of these patients, who underwent a complex procedure for in-stent thrombosis, required a prolonged hospitalization due to a stressinduced cardiomyopathy. Conclusion: Endovascular treatment of CCSVI in MS patients is a safe procedure when performed on an outpatient basis. Cardiac monitoring is essential to permit detection and rapid treatment of patients with procedure-induced arrhythmias. Post-procedure ultrasound is recommended to detect venous thrombosis. In addition, consideration should be given to performing complex re-interventions in a hospital given the complication risk in this sub-population of patients
ISSN: 1051-0443

5. Zamboni P, Galeotti R, Weinstock-Guttman B, et al. Endovascular treatment of chronic cerebrospinal venous insufficiency in the management of multiple sclerosis. Vascular 2010; 18: S81.
Abstract: Background: Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by stenoses of the internal jugular veins or the azygous vein, or both. It has been recently reported that this condition contributes to severe dis-regulation of the physiologic mechanisms of cerebral venous outflow in patients with multiple sclerosis (MS). Endovascular treatment (EVT) was demonstrated to be a safe and effective CCSVI treatment, but only in an unblinded clinical evaluation. Methods: We designed an open-label, magnetic resonance imaging (MRI)-blinded, two-center, randomized, EVT intervention parallel-group, 12-month study (EVTMS) after an initial cross-sectional (CVIMS) study. CIVMS enrolled 16 relapsing-remitting MS patients (8 from Ferrara, Italy and 8 from Buffalo, NY). All 16 patients who completed the CVIMS study and presented severe Doppler venous hemodynamic (VH) anomalies accepted participation in the EVT intervention prospective study (EVTMS). Half of the cohort, the early intervention group (4 from Buffalo and 4 from Italy), was randomly selected to have the EVT procedure in Italy at 3 months, whereas 6 patients comprised the delayed control intervention group (late group) at 6 months; 2 patients were followed-up without any EVT. The EVT procedure consists of selective venography complemented by balloon dilatation when significant stenoses are detected. All patients will be prospectively evaluated at 3, 6, 9, and 12 months with ultrasound imaging, MRI, and clinical examinations. Results: For the CVIMS cross-sectional study, mean age at baseline was 36.1+/-7.3 years, mean disease duration was 7.5+/-1.9 years, and median Expanded Disability Status Scale (EDSS) was 2.5. The mean number of gadolinium-active lesions at baseline was 0.38 +/- 1.5. The mean number of T2 lesions was 27.1 +/- 10.5. Median of VH of CCSVI was 4 (range, 2-5). The six MS patients investigated and none of the HCs met the VH criteria for CCSVI (P 2
Background: C hronic cerebrospinal venous insufficiency (CCSVI) is characterized by stenosies of the internal jugular veins (IJVs) and/or the azygous vein. This condition contributes to disregulation of the physiologic mechanisms of cerebral venous return in patients with multiple sclerosis (MS). Endovascular treatment (EVT) of CCS VI in MS was never evaluated in blinded condition. Methods: We designed a MRI-blinded, randomized, EVT intervention parallel-group, 12-month study (EVT-MS). Fifteen relapsingremitting MS patients were enrolled. The cohort was subset into early intervention group

(EIG) were randomly selected to have the EVT procedure at baseline, whereas seven patients (delayed intervention group, DIG) 6 months later. The EVT procedure consists of selective venography complemented by balloon dilatation when significant stenoses are detected. Results: The EVT-MS is safe and well tolerated because we did not register major complications, and the treatment was feasible in local anesthesia in a day surgery setting. R ate of restenosis/ineffective EVT was 29% limitedly to the IJVs. The risks of neurological relapses of the associated MS, although not significant for the dimension of the sample, were higher in the DIG respect to the EIG: four cases versus one case, respectively, OR = 14, 95% C I 0.9435 to 207.74. The analysis of the blinded MRI measures are under way from the independent statistician. Conclusions: The EVT-MS is a safe and well-tolerated procedure, feasible in daily clinical setting. This study should provide valuable data on preliminary efficacy of EVT for CCSVI associated to MS
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6. Zamboni P, Galeotti R, Weinstock-Guttman B, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency in multiple sclerosis: A longitudinal, magnetic resonance imaging, blinded pilot study. J Vasc Surg 2010; 51: 794.
Abstract: Background: Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by stenoses of the internal jugular veins or the azygous vein, or both. It has been recently reported that this condition contributes to severe dis-regulation of the physiologic mechanisms of cerebral venous outflow in patients with multiple sclerosis (MS). Endovascular treatment (EVT) was demonstrated to be a safe and effective CCSVI treatment, but only in an unblinded clinical evaluation. Methods: We designed an open-label, magnetic resonance imaging (MRI)-blinded, two-center, randomized, EVT intervention parallel-group, 12-month study (EVTMS) after an initial cross-sectional (CVIMS) study. CIVMS enrolled 16 relapsing-remitting MS patients (8 from Ferrara, Italy and 8 from Buffalo, NY). All 16 patients who completed the CVIMS study and presented severe Doppler venous hemodynamic (VH) anomalies accepted participation in the EVT intervention prospective study (EVTMS). Half of the cohort, the early intervention group (4 from Buffalo and 4 from Italy), was randomly selected to have the EVT procedure in Italy at 3 months, whereas 6 patients comprised the delayed control intervention group (late group) at 6 months; 2 patients were followed-up without any EVT. The EVT procedure consists of selective venography complemented by balloon dilatation when significant stenoses are detected. All patients will be prospectively evaluated at 3, 6, 9, and 12 months with ultrasound imaging, MRI, and clinical examinations. Results: For the CVIMS cross-sectional study, mean age at baseline was 36.1+/-7.3 years, mean disease duration was 7.5+/-1.9 years, and median Expanded Disability Status Scale (EDSS) was 2.5. The mean number of gadolinium-active lesions at baseline was 0.38 +/- 1.5. The mean number of T2 lesions was 27.1 +/- 10.5. Median of VH of CCSVI was 4 (range, 2-5). The six MS patients investigated and none of the HCs met the VH criteria for CCSVI (P

Trials

Study 1:
Title: Multi-center Registry for CCSVI Testing and Treatment
Recruitment: Recruiting
Study Results: No Results Available
Conditions: CCSVI|Chronic Cerebrospinal Venous Insufficiency|Venous Malformations|Multiple Sclerosis
Interventions:
Study Types: Observational
Completion Date: September 2015
URL: http://ClinicalTrials.gov/show/NCT01205633

Study 2:
Title: Evaluation of Angioplasty in the Treatment of Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Multiple Sclerosis
Interventions: Procedure: Angioplasty|Other: Observation
Study Types: Interventional
Completion Date: August 2013
URL: http://ClinicalTrials.gov/show/NCT01201707

Study 3:
Title: Study To Evaluate Treating Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis Patients
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Multiple Sclerosis
Interventions: Procedure: Venoplasty|Procedure: Sham procedure (non-treatment)
Study Types: Interventional
Completion Date: September 2011
URL: http://ClinicalTrials.gov/show/NCT01089686

Study 4:
Title: Endovascular Treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI)
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Multiple Sclerosis
Interventions: Procedure: balloon angioplasty and/or stenting|Procedure: balloon angioplasty and/or stenting
Study Types: Interventional
Completion Date: December 2010
URL: http://ClinicalTrials.gov/show/NCT01264848

Trials in Buffalo:

CTEVD-study: diagnostische studie.
This is a comprehensive, blinded study of over 1,000 patients with multiple sclerosis (MS) and other related diseases. Researchers use information from magnetic resonance imaging (MRI) of the brain and neck veins to test the controversial chronic cerebrospinal venous insufficiency (CCSVI) theory. They also study the results of Doppler ultrasound tests that monitor the rate of blood flow to and from the brain. Using blood samples, they look at genetic and environmental factors that may cause MS and also review the participants' responses to a detailed environmental questionnaire. Finally, each subject has a clinical examination by an MS Specialist from the Baird MS Center, part of the Jacobs Neurological Institute, University at Buffalo.
The results of the first 500 subjects were presented by Dr. Robert Zivadinov and his research team at the AAN annual conference in March, 2010. The study is continuing and the results are under submission in major neurological journals.
With data on over 500 MS patients and controls, BNAC 's CTEVD study is one of the largest in the world and our researchers and technicians gained considerable experience studying CCSVI. This unique expertise is critical in the analysis of how constriction of venous blood flow relat

PREMiSe (Prospective Randomized Endovascular therapie in Multiple Sclerosis).
BNAC is conducting this research in collaboration with the University at Buffalo's Department of Neurosurgery. The **study is testing safety and efficacy of the balloon** angioplasty in 30 multiple sclerosis (MS) participants that are followed over 6 months. The results are expected by summer of 2011. As the first IRB approved placebo-controlled clinical trial to test the safety and efficacy of CCSVI treatment, this study is receiving international attention from among all the medical and patient communities interested in MS.

VU: nieuws over het onderzoek bij de VU.