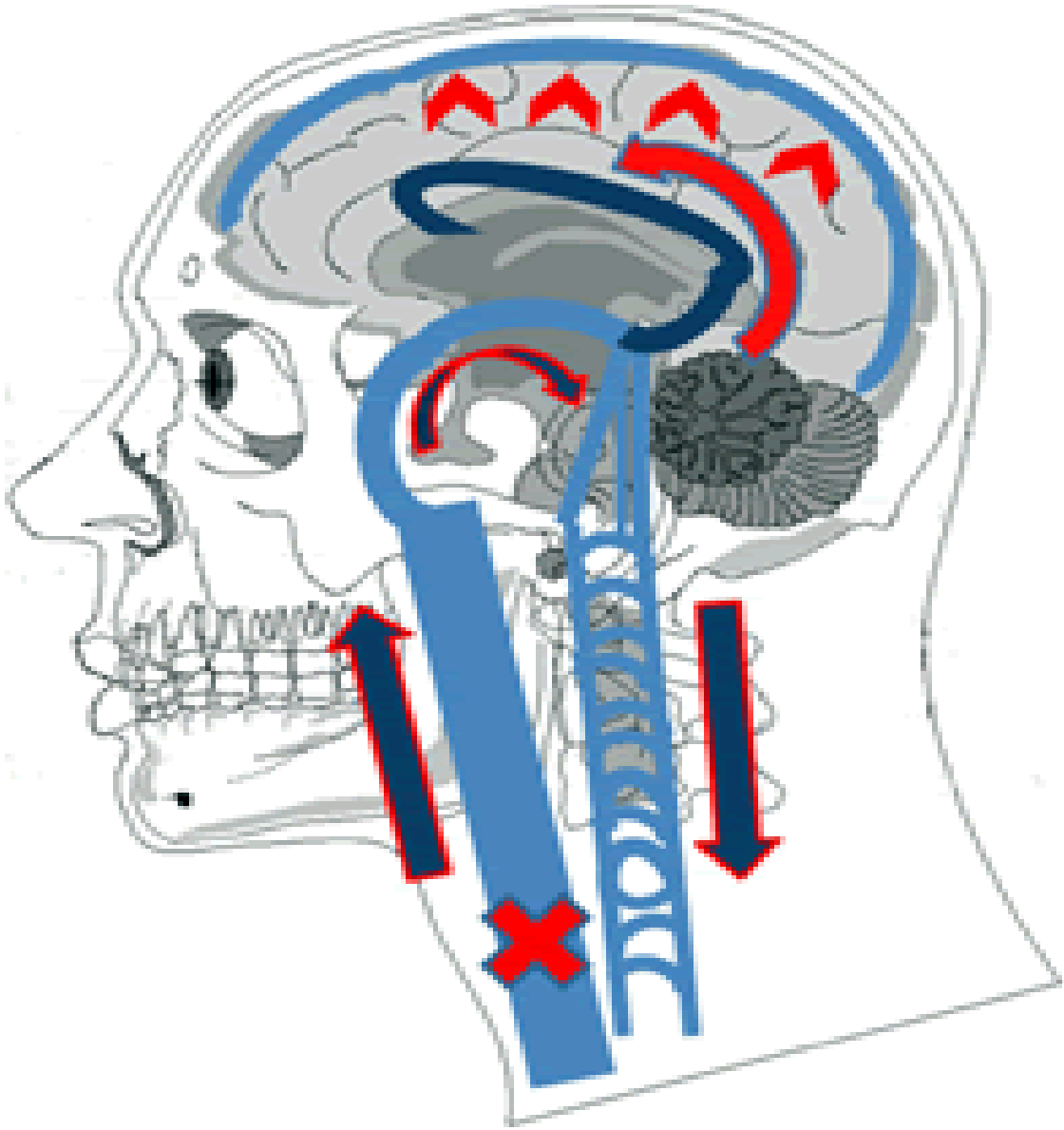
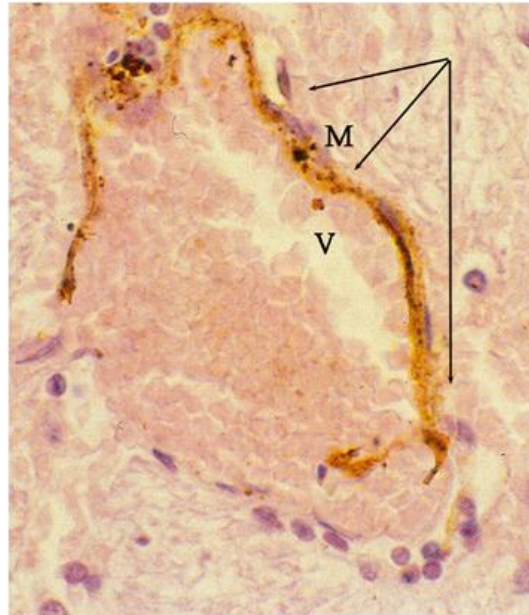


Multiple Sclerosis CCSVI

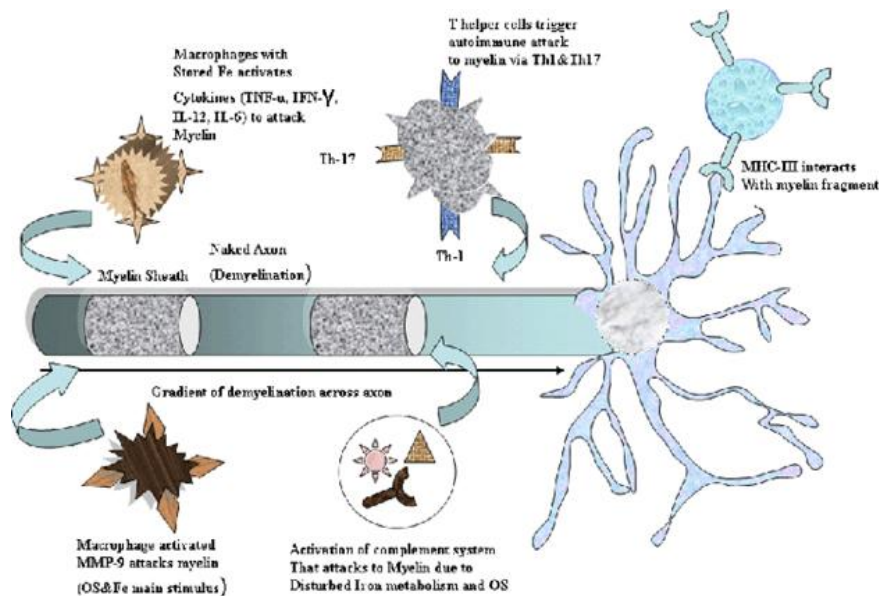


Introductions

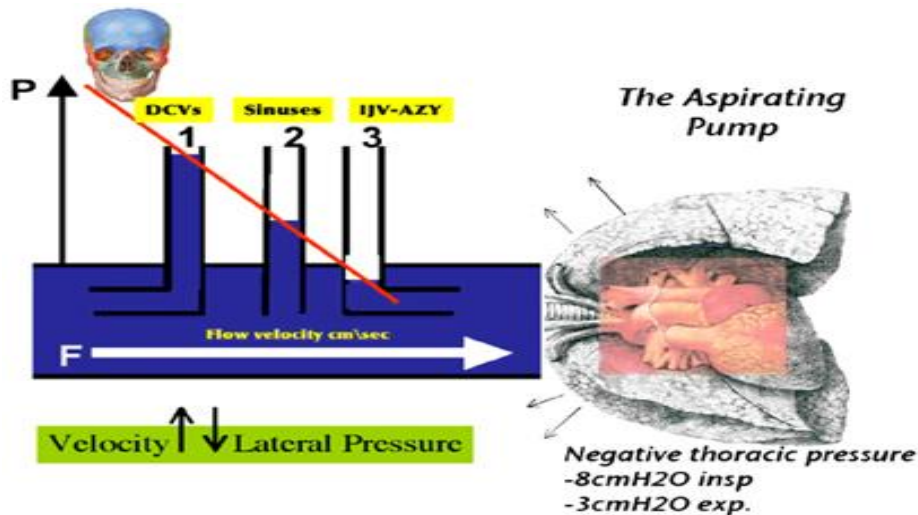
Anomalous venous blood flow and iron deposition in multiple sclerosis Venous hemodynamics and iron stores in MS. Journal of Cerebral Blood Flow & Metabolism 29, 1867-1878 (December 2009) | doi:10.1038/jcbfm.2009.180- Ajay Vikram Singh and Paolo Zamboni



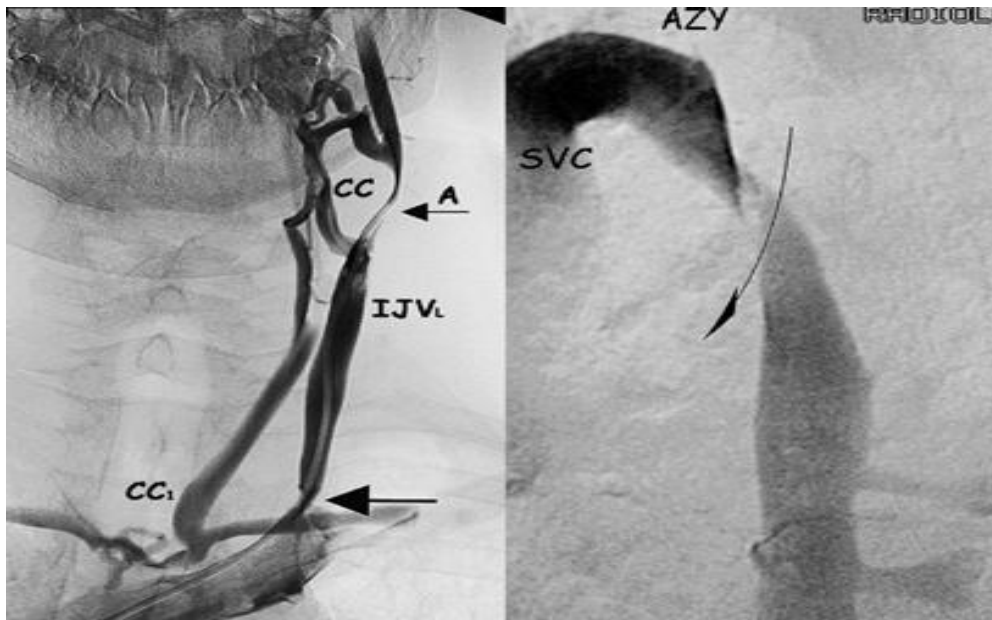
Histology of a brain MS plaque (hematoxylin-eosin 50). The figure depicts a streak of blood (arrows) encircling the wall of a vein (V) at the center of an MS brain plaque. Heme iron triggers macrophages (infiltration, demonstrated by the presence of iron-laden phagocyte (M



Autoimmunity attack to myelin. The role of major cells from immune cascade those attack and damage to the myelin sheath under autoimmune modulation across cerebrospinal region, triggered by iron overload and oxidative stress (IL, interleukin; Th, T-helper cells; MMP, matrix metallo proteinase; MHC, major histocompatibility complex; TNF-, tumor necrosis factor-; IFN-, interferon-)



Physiology of cerebral venous return. The blood leaves the brain by using the back propulsion of the residual arterial pressure (*vis a tergo*), much more important in the cerebral veins, complemented by antegrade postural and respiratory mechanisms (*vis a fronte*), which has a major function in the dural sinuses and in the jugular and azygos vein (IJV-AZ). In fact, the blood flow velocity is higher close to the chest, due to the negative thoracic pressure gradient, increased by inspiration. According to the Bernoulli law, by increasing the blood flow velocity there is a corresponding reduction of the lateral pressure resulting in a natural aspiration of the deep cerebral veins (DCVs) into the sinuses, and finally into the main outflow extracranial pathways, IJV-AZ.



Extracranial venous stenosis associated to MS (CCSVI). Selective venography in the course of CCSVI associated to MS. Left: proximal stenosis of the left IJV (arrow) with agenesia more distally (A). Intra–extra cranial collateral circle (CC1) represented by condylar veins shunts the double block, whereas the agenesia is bypassed by an extracranial collateral (CC). Right: Twisting of the descending segment of the AZ just below the arch communicating with the superior vena cava (SVC).

Epidemiology of multiple sclerosis in Kuwait: new trends in incidence and prevalence. .Alshubaili AF, Alramzy K, Ayyad YM, Gerish Y. Eur Neurol. 2005;53(3):125-31. Epub 2005 Apr 28.

The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The EDSS replaced the previous Disability Status Scales which used to bunch people with MS in the lower brackets.

The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are:

- pyramidal (ability to walk)
- cerebellar (coordination)
- brainstem (speech and swallowing)
- sensory (touch and pain)
- bowel and bladder
- visual
- cerebral
- other

EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulatory.

The National MS Society of America convened an international panel chaired by Professor W. Ian McDonald to update the Poser Criteria for the diagnosis of MS and in April 2001 recommended the following criteria which makes use of MRI imaging in making diagnostic conclusions:

Clinical Presentation	Additional Data Needed
2 or more attacks (relapses) 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
2 or more attacks 1 objective clinical lesion	Dissemination in space, demonstrated by: MRI or a positive CSF and 2 or more MRI lesions consistent with MS or further clinical attack involving different site
1 attack 2 or more objective clinical lesions	Dissemination in time, demonstrated by: MRI or second clinical attack
1 attack 1 objective clinical lesion monosymptomatic presentation	Dissemination in space by demonstrated by: MRI or positive CSF and 2 or more MRI lesions consistent with MS <i>and</i> Dissemination in time demonstrated by: MRI or second clinical attack
Insidious neurological progression suggestive of MS primary progressive MS	Positive CSF <i>and</i> Dissemination in space demonstrated by: MRI evidence of 9 or more T2 brain lesions or 2 or more spinal cord lesions or 4-8 brain and 1 spinal cord lesion or positive VEP with 4-8 MRI lesions or positive VEP with <4 brain lesions plus 1 spinal cord lesion <i>and</i> Dissemination in time demonstrated by: MRI or continued progression for 1 year

The Expanded Disability Status Scale (EDSS) and Multiple Sclerosis

.Julie Stachowiak, Ph.D

How Is an EDSS Score Calculated?

The score is based upon neurological testing and examination of functional systems (FS), which are areas of the central nervous system which control bodily functions. The functional systems are:

- Pyramidal (ability to walk)
- Cerebellar (coordination)
- Brain stem (speech and swallowing)
- Sensory (touch and pain)
- Bowel and bladder functions
- Visual
- Mental
- Other (includes any other neurological findings due to MS)

These rankings are especially important in the “less severe” lower numbers of the scale, when a patient is still ambulatory, yet experiencing some abnormal signs or disability in other areas.

The Expanded Disability Status Scale (EDSS)

- 0.0:** Normal neurological exam.
- 1.0:** No disability, but minimal signs in one functional system (FS) are present.
- 1.5:** No disability, but minimal signs in more than one FS are present.
- 2.0:** Minimal disability in one FS is present.
- 2.5:** There is mild disability in one FS or minimal disability in two FS.
- 3.0:** There is moderate disability in one FS or mild disability in three or four FS. However, the person is still fully ambulatory.
- 3.5:** The person is fully ambulatory, but has moderate disability in one FS and mild disability in one or two FS; or moderate disability in two FS; or mild disability in five FS.
- 4.0:** The person is fully ambulatory without aid, and is up and about most of the day (12 hours) despite relatively severe disability. He or she is able to walk 500 meters without aid or rest.
- 4.5:** The person is fully ambulatory without aid, and is up and about much of day. He or she is able to work a full day, but may otherwise have some limitations of full activity or require minimal assistance. This is considered relatively severe disability. Able to walk 300 meters without aid.
- 5.0:** The person is able to walk 200 meters without aid or rest. Disability impairs full daily activities, such as working a full day without special provisions.
- 5.5:** The person is able to walk 100 meters without aid or rest. Disability precludes full daily activities.
- 6.0:** The person needs intermittent or unilateral constant assistance (cane, crutch or brace) to walk 100 meters with or without resting.
- 6.5:** The person needs constant bilateral support (cane, crutch or braces) to walk 20 meters without resting.
- 7.0:** The person is unable to walk beyond five meters even with aid, and is essentially restricted to a wheelchair. However, he or she wheels self and transfers alone, and is active in wheelchair about 12 hours a day.
- 7.5:** The person is unable to take more than a few steps and is restricted to wheelchair, and may need aid to transfer. He or she wheels self, but may require a motorized chair for a full day's activities.
- 8.0:** The person is essentially restricted to bed, a chair or a wheelchair, but may be out of bed much of day. He or she retains self care functions and has generally effective use of arms.
- 8.5:** The person is essentially restricted to bed much of day, but has some effective use of arms and retains some self care functions.
- 9.0:** The person is confined to bed, but still able to communicate and eat.
- 9.5:** The person is totally helpless and bedridden and is unable to communicate effectively or eat and swallow.
- 10.0:** Death due to MS.

Fatigue Severity Scale (FSS) scoring

The Fatigue Severity Scale (FSS) is a method of evaluating fatigue in multiple sclerosis and other conditions (including Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) and Systemic Lupus Erythmatosis (SLE).

The Fatigue Severity Scale (FSS) is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. Essentially, the FSS consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with this measure is its subjectivity.

Here is an example FSS questionnaire containing nine statements that attempt to explore severity of fatigue symptoms. The subject is asked to read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you

- A low value (e.g., 1); indicates strong disagreement with the statement, whereas a high value (e.g., 7); indicates strong agreement.
- It is important that you circle a number (1 to 7); for every question.

FSS Questionnaire

During the past week, I have found that:	Score						
	Disagree <-----> Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
Total Score							

The scoring is done by calculating the average response to the questions (adding up all the answers and dividing by nine).

People with depression alone score about 4.5. But people with fatigue related to MS, SLE or CFIDS average about 6.5.

Total score of less than 36 suggests that you may not be suffering from fatigue.

A total score of 36 or more suggests that you may need further evaluation by a physician.

(Multiple Sclerosis Impact Scale (MSIS-29

Background and aim: The psychometric properties of rating scales are sample dependent and need evaluations in different samples. The Multiple Sclerosis Impact Scale (MSIS-29), a new patient based rating scale for multiple sclerosis (MS) was predominantly developed from a community based sample derived from the MS Society.

- The following questions ask for your views about the impact of MS on your day-to-day life **during the past two weeks**
- For each statement, please **circle** the **one** number that **best** describes your situation
- Please answer **all** questions

In the <u>past two weeks</u> , how much has your MS ...limited your ability to	Not at all	A little	Moderately	Quite a bit	Extremely
---	---------------	-------------	------------	----------------	-----------

.1	?Do physically demanding tasks	1	2	3	4	5
.2	?(Grip things tightly (e.g. turning on taps	1	2	3	4	5
.3	?Carry things	1	2	3	4	5
.4	?Problems with your balance	1	2	3	4	5
.5	?Difficulties moving about indoors	1	2	3	4	5
.6	?Being clumsy	1	2	3	4	5
.7	?Stiffness	1	2	3	4	5
.8	?Heavy arms and/or legs	1	2	3	4	5
.9	?Tremor of your arms or legs	1	2	3	4	5
.10	?Spasms in your limbs	1	2	3	4	5
.11	?Your body not doing what you want it to do	1	2	3	4	5
.13	?Limitations in your social and leisure activities at home	1	2	3	4	5
.14	?Being stuck at home more than you would like to be	1	2	3	4	5
.15	?Difficulties using your hands in everyday tasks	1	2	3	4	5
.16	Having to cut down the amount of time you spent on work or other daily ?activities	1	2	3	4	5
.17	?(.Problems using transport (e.g. car, bus, train, taxi, etc	1	2	3	4	5
.18	?Taking longer to do things	1	2	3	4	5
.19	Difficulty doing things spontaneously (e.g. going out on the spur of the ?(moment	1	2	3	4	5
.20	?Needing to go to the toilet urgently	1	2	3	4	5
.21	?Feeling unwell	1	2	3	4	5
.22	?Problems sleeping	1	2	3	4	5
.23	?Feeling mentally fatigued	1	2	3	4	5
.24	?Worries related to your MS	1	2	3	4	5
.25	?Feeling anxious or tense	1	2	3	4	5
.26	?Feeling irritable, impatient, or short tempered	1	2	3	4	5
.27	?Problems concentrating	1	2	3	4	5
.28	?Lack of confidence	1	2	3	4	5
.29	?Feeling depressed	1	2	3	4	5

Please check that you have circled ONE number for EACH question

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The researchers will test the possibility that the symptoms of MS result from narrowing of the primary veins outside the skull, a condition called "chronic cerebrospinal venous insufficiency," or CCSVI.

CCSVI is a complex vascular condition discovered and described by Paolo Zamboni, M.D., from Italy's University of Ferrara. In the original Italian patients, CCSVI was found to be strongly associated with MS, increasing the risk of developing MS by 43 fold.

This narrowing restricts the normal outflow of blood from the brain, causing alterations in the blood flow patterns within the brain that eventually causes injury to brain tissue and degeneration of neurons.

Multiple sclerosis (MS) is primarily an autoimmune disorder of unknown origin. Iron overload and oxidative stress as surrounding cause that leads to immunomodulation in chronic MS. Iron overload has been demonstrated in MS lesions, as a feature common with other neurodegenerative disorders.

However, the recent description of chronic cerebrospinal venous insufficiency (CCSVI) associated to MS, with significant anomalies in cerebral venous outflow hemodynamics, permit to propose a parallel with chronic venous disorders (CVDs) in the mechanism of iron deposition.

Abnormal cerebral venous reflux is peculiar to MS, and was not found in a miscellaneous of patients affected by other neurodegenerative disorders characterized by iron stores, such as Parkinson's, Alzheimer's, amyotrophic lateral sclerosis.

Several recently published studies support the hypothesis that MS progresses along the venous vasculature. The peculiarity of CCSVI-related cerebral venous blood flow disturbances, together with the histology of the perivenous spaces and recent findings from advanced magnetic resonance imaging techniques, support the hypothesis that iron deposits in MS are a consequence of altered cerebral venous return and chronic insufficient venous drainage. **[Anomalous venous blood flow and iron deposition in multiple sclerosis. J Cereb Blood Flow Metab. 2009 Dec;29(12):1867-78. Epub 2009 Sep 2Singh AV, Zamboni P.]**

A new nosologic vascular pattern that is defined by chronic cerebrospinal venous insufficiency (CCSVI) has been strongly associated with multiple sclerosis. The picture is characterized by significant obstacles of the main extracranial cerebrospinal veins, the jugular and the azygos system, and by the opening of substitute circles. The significance of collateral circle is still neglected. To the contrary, substitute circles are alternative pathways or vicarious venous shunts, which permit the drainage and prevent intracranial hypertension. In accordance with the pattern of obstruction, even the intracranial and the intrarachidian veins can also become substitute circles, they permit redirection of the deviated flow, piping the blood towards available venous segments outside the central nervous system. We review the complex gross and radiological anatomy of collateral circulation found activated by the means of EchoColor-Doppler and selective venography in the event of CCSVI, focusing particularly on the suboccipital cavernous sinus (SCS), the condylar venous system, the pterygoid plexus, the thyroid veins, and the emiazygos-lumbar venous anastomosis with the left renal vein.

Venous Collateral Circulation of the Extracranial Cerebrospinal Outflow Routes pp.204-212 (9) Authors: Paolo Zamboni, Giuseppe Consorti, Roberto Galeotti, Sergio Giancesini, Erica Menegatti, Giovanna Tacconi, Francesco Carinci -Current Neurovascular Research Volume 6 Issue 3 ISSN: 1567-2026

The extracranial venous outflow routes in clinically defined multiple sclerosis (CDMS) have not previously been investigated. CDMS is strongly associated with CCSVI, a scenario that has not previously been described, characterised by abnormal venous haemodynamics determined by extracranial multiple venous strictures of unknown origin. The location of venous obstructions plays a key role in determining the clinical course of the disease. **[Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009 Apr;80(4):392-9. Epub 2008 Dec 5.Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S, Bartolomei I, Salvi F.]**

To evaluate patency and clinical outcome in patients treated with endovascular recanalization and stent placement for chronic iliac vein occlusions. Endovascular recanalization and stent placement is a safe and effective treatment for occluded iliac veins and adjacent segments. Clinical midterm results are encouraging. Recanalized and stented segments remain patent in the majority of patients after 2 years. Endovascular treatment can ease symptoms and prevent further deterioration of patients with post-thrombotic syndrome. **[Chronic iliac vein occlusion: midterm results of endovascular recanalization. J Endovasc Ther. 2009 Aug;16(4):483-91. Kölbel T, Lindh M, Akesson M, Wassélius J, Gottsäter A, Ivancev K.]**

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 azygos (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. **[A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg. 2009 Dec;50(6):1348-58.e1-3. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Gianesini S, Bartolomei I, Mascoli F, Salvi F.]**