Vascular aspects of multiple sclerosis

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Three types of vascular dysfunction have been described in multiple sclerosis (MS). First, findings from epidemiological studies suggest that patients with MS have a higher risk for ischaemic stroke than people who do not have MS. The underlying mechanism is unknown, but might involve endothelial dysfunction secondary to inflammatory disease activity and increased plasma homocysteine concentrations. Second, patients with MS have global cerebral hypoperfusion, which might predispose them to the development of ischaemic stroke. The widespread decrease in perfusion in normal-appearing white matter and grey matter in MS seems not to be secondary to axonal degeneration, but might be a result of reduced axonal activity, reduced astrocyte energy metabolism, and perhaps increased blood concentrations of endothelin-1. Data suggest that a subtype of focal MS lesions might have an ischaemic origin, and there seems to be a link between reduced white matter perfusion and cognitive dysfunction in MS. Third, the pathology of MS might be the consequence of a chronic state of impaired venous drainage from the CNS, for which the term chronic cerebrospinal venous insufficiency (CCSVI) has been coined. A number of recent vascular studies do not support the CCSVI theory, but some elements of CCSVI might be explained by slower cerebral venous blood flow secondary to the reduced cerebral perfusion in patients with MS compared with healthy individuals.

Introduction

The pathological hallmarks of multiple sclerosis (MS) are focal lesions, characterised by demyelination, inflammation, axonal injury and gliosis, and diffuse axonal degeneration throughout the CNS.1 In some regions, MS prevalence can exceed 100 per 100 000 people,2 and worldwide up to 2 million people are estimated to be affected.1 The peak age of onset is between 20 and 40 years,3 and disease progression often leads to severe neurological disability. The exact cause and pathogenesis of MS are unknown. The most widely accepted hypothesis is that MS is an autoimmune disease that leads to destruction of CNS myelin. Anti-myelin T-cell-mediated inflammatory responses are believed to have a crucial role in the development of focal lesions.4 However, the underlying mechanism of the widespread axonal degeneration is not yet fully understood.

In recent years, several studies have reported vascular abnormalities in patients with MS. First, epidemiological data suggest that patients with MS might have an increased risk of developing ischaemic stroke. Second, imaging studies in patients with MS suggest a decrease in cerebral perfusion that affects widespread areas including the normal-appearing white matter (NAWM). Third, MS has been associated with reduced CNS venous blood drainage, which is referred to as chronic cerebrospinal venous insufficiency (CCSVI). The question arises as to whether these findings might be associated with each other. Does decreased perfusion in NAWM promote the development of ischaemic lesions? Could impaired CNS venous blood drainage be the reason for the decreased cerebral perfusion or is the reverse true? In this Review, we provide a summary of these three vascular abnormalities described in MS, and discuss their pathophysiological significance and possible mutual relation.

MS and ischaemic stroke

Cardiovascular events in MS

The cause of death in patients with MS has been the subject of several epidemiological studies.5–10 Most of these studies distinguished only between deaths associated with MS and non-MS-related deaths, and provided no further information. Two nationwide Danish studies that investigated category-specific mortality reported that patients with MS had about a 30% higher risk of dying from cardiovascular disease than did the age-matched general population11,12 but did not differentiate between the various types of cardiovascular events. A study in south Wales, UK, of patients with MS reported only a 6% higher risk of dying from cardiovascular disease compared with healthy controls, but cerebrovascular disease was excluded from this analysis.13 The excess cardiovascular mortality in patients with MS could not be explained at the time, and the findings were mainly attributed to lower levels of physical activity.

Two large studies revealed more detailed information on the occurrence of cardiovascular disease in people with MS. First, Allen and colleagues14 compared the prevalence of ischaemic heart disease, myocardial infarction, and ischaemic stroke among 9949 patients with MS and 19 898 people without MS, matched for age, sex, ethnic origin, and insurance, who were all between 40 and 85 years of age. They used the Statewide Planning and Research Cooperative System dataset of over 15 million hospital admissions in New York City from 1988 to 2002. Multivariate logistic regression was used to compare vascular disease outcomes while controlling for demographic and clinical factors. Patients with MS had decreased rates of hospital admissions for ischaemic heart disease (odds ratio 0·58, 95% CI 0·51–0·66) and myocardial infarction (0·78, 0·64–0·96) but were more likely to be admitted to hospital for ischaemic stroke (1·66, 1·33–2·09) than people without MS. Second, Christiansen and co-workers15 did a large
population-based cohort study that included 13,963 Danish citizens with MS and 66,407 age-matched and sex-matched controls. They calculated adjusted incidence rate ratios (IRR) with data from the Danish National Registry of Patients over a 30-year period (1977–2006). MS was associated with an increased risk of hospital admissions for ischaemic stroke (IRR 1.92, 95% CI 1.27–2.71), myocardial infarction (1.84, 1.28–2.65), and heart failure (1.92, 1.27–2.90) in the first year after diagnosis. During the entire 30-year-long follow-up period the excess risk for ischaemic stroke (IRR 1.23, 95% CI 1.10–1.38) and heart failure (1.53, 1.37–1.71) persisted. By contrast, Fleming and Blake reported that patients with MS were less likely to be admitted to hospital for both ischaemic heart disease and ischaemic stroke. However, this study was small, and the results were probably an underestimation because only patients older than 65 years of age were included, and there were methodological limitations—e.g., patients could only be diagnosed with up to five diseases per hospital discharge. Although probably not noticeable on an individual basis in daily practice, and although epidemiological studies must be interpreted with caution, the seemingly well designed population-based studies done in New York and Denmark suggest that patients with MS have an increased risk of ischaemic stroke.

Possible underlying mechanisms
Data on possible biological mechanisms underlying vascular disease in MS are scarce. Among the traditional vascular risk factors, smoking and reduced physical activity are most frequently reported in patients with MS. By contrast, arterial hypertension, diabetes mellitus, dyslipidaemia, and obesity generally do not seem to be associated with MS. Atrial fibrillation and flutter, which are common causes of cardioembolic stroke, are also not more prevalent in patients with MS than in the general population.

Inflammation is widely accepted to play an integral part in the pathogenesis of atherosclerosis. Endothelial dysfunction is an early step towards overt atherosclerosis and the immune system seems to be highly involved in both processes. Endothelial dysfunction has been described in the very early stage of rheumatoid arthritis, probably as a result of inflammatory disease activity. Rheumatoid arthritis is an autoimmune disease in which increased cardiovascular morbidity and mortality has been noted. Alterations in endothelial function, as well as platelet activation and thrombophilia, have been reported in MS. Moreover, oxidative stress contributes to the development of endothelial dysfunction. Higher amounts of systemic and CNS oxidative stress have been reported in patients with MS than in healthy controls. The concentration of plasma homocysteine, which is believed to be an independent cardiovascular risk factor, is also raised in patients with MS. The cause of the increase in homocysteine concentration is unknown, but it occurs independently of serum concentrations of vitamin B12, vitamin B6, or folate.

There is evidence that hyperhomocysteinaemia can cause endothelial dysfunction, even at moderately increased concentrations of homocysteine.

The above evidence suggests that the increased frequency of ischaemic stroke in MS might be mediated through converging inflammatory pathways, oxidative stress, and raised homocysteine concentrations leading to endothelial dysfunction.

Cerebral hypoperfusion in MS
Reduced cerebral blood flow

Another factor that might promote the development of ischaemic brain lesions in individuals with MS is globally decreased cerebral perfusion. Cerebral perfusion is defined as the volume of blood flowing through a given volume of tissue per unit time. Mathematically, it consists of three parameters: cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time. Single-photon emission computed tomography and PET studies have shown that CBF is decreased in both the grey and white matter of patients with MS. Cerebral perfusion measurements with MRI have long remained qualitatively challenging, but technical progress with more accurate imaging and processing has renewed interest in this field over the past decade.

Using dynamic susceptibility contrast-enhanced MRI (DSC-MRI), Law and colleagues found markedly decreased CBF and prolonged mean transit time throughout the NAWM of the brain in 17 patients with relapsing-remitting MS compared with 17 control individuals. Adhya and colleagues subsequently studied the regional pattern of perfusion in NAWM in 11 patients with relapsing-remitting MS, 11 patients with primary progressive MS, and 11 control individuals. They concluded that both CBF and CBV were substantially decreased in all NAWM regions in patients with either form of MS compared with control individuals. Similar findings of reduced cerebral perfusion in individuals with MS can be obtained with the arterial spin-labelling technique, which is a non-invasive MRI perfusion-weighted method (see figure 1 for an example).

There are several reports of a similar amount of hypoperfusion in the cerebral cortex and subcortical grey matter of patients with MS. This hypoperfusion might be caused by the same mechanisms that underlie hypoperfusion in NAWM or might result from a disconnection between the cerebral cortex and subcortical nuclei caused by white matter damage in the centrum semiovale. The reduced cortical perfusion in MS has similar features to those found inBinswanger’s chronic ischaemic leuкоencephalopathy. Varga and colleagues used DSC-MRI to assess CBF in the cerebral NAWM, thalamus, and putamen in 12 patients with a clinically isolated syndrome, 12 patients with early relapsing-remitting MS (within
5 years of first symptoms), and 12 healthy control individuals. CBF was decreased in the NAWM of patients with clinically isolated syndrome and those with relapsing-remitting MS compared with control individuals. These results suggest that decreased CBF in NAWM is already present in the very early stages of the disease. Compared with patients with clinically isolated syndrome and healthy control individuals, patients with relapsing-remitting MS also had significantly decreased CBF in the putamen, which might suggest a continuum of decreases in tissue perfusion, beginning in the white matter and spreading to grey matter as the disease progresses. However, this hypothesis needs to be confirmed.

Disruption of the blood–brain barrier occurs before or during the development of focal MS lesions and can be visualised as local gadolinium-enhancing areas on T1-weighted MRI. Compared with NAWM, DSC-MRI has revealed two patterns of perfusion changes in gadolinium-enhancing lesions. Diffuse enhancing areas were characterised by increases in CBF and CBV. By contrast, in lesions that developed ring enhancement, CBF and CBV changes similar to non-ring-enhancing lesions were seen only in the ring tissue, whereas inside the ring there was a decrease in CBF, suggestive of a central ischaemic zone. Some patients have developed new focal MS lesions with diffusion-weighted MRI characteristics similar to those found with acute ischaemia. These preliminary data suggest that focal ischaemia might play a part in the development of a subcategory of focal MS lesions.

Possible underlying mechanisms
Cerebral hypoperfusion in patients with MS was first assumed to be secondary to a reduced vascular inflow in the context of focal perivascular inflammatory MS lesions. However, this theory is unlikely to explain the hypoperfusion because if this were the case the inflow should produce a patchy pattern of focal CBF decreases instead of the diffuse pattern of reduced perfusion throughout the NAWM that is seen in patients with MS.

Cerebral hypoperfusion in patients with MS might be secondary to axonal degeneration, leading to a decreased metabolic demand. Saindane and colleagues studied the relation between perfusion-weighted and diffusion-weighted MRI features in the normal-appearing corpus callosum of patients with relapsing-remitting MS and control individuals. Decreased perfusion was positively correlated with decreased mean diffusivity but not with fractional anisotropy. These findings do not support the hypothesis that reduced cerebral perfusion in the NAWM of patients with MS is secondary to axonal degeneration, a situation that would be characterised by increased mean diffusivity and decreased fractional anisotropy. However, this finding does not exclude the possibility that NAWM hypoperfusion in MS could be secondary to reduced axonal activity.

In normal conditions, $K^+$ released at the nodes of Ranvier during axonal discharge is soaked up by astrocytes through inward-rectifying $K^+$ channels (Kir), mainly Kir4.1. $K^+$ taken up by astrocytes is intracellularly redistributed and released at perivascular endfeet through Ca²⁺-activated $K^+$ channels in a process leading to arteriolar vasodilation. Decreased axonal activity might reduce axonal $K^+$ release and subsequent release in the perivascular spaces, possibly leading to a state of cerebral hypoperfusion. Energy metabolism of astrocytes seems to be dysfunctional in MS. Astrocytes in patients with MS are deficient in β2-adrenergic receptors, which regulate glycogenolysis, and have reduced phosphocreatine metabolism caused by decreased cytosolic creatine kinase B concentrations and activity. A highly energy-consuming activity at the astrocytic endfeet during electrogenesis at the nodes of Ranvier is the action of the astrocytic Na⁺/$K^+$

![Figure 1: Cerebral perfusion in a patient with MS and a healthy individual](image-url)
the perivascular space through Ca²+-activated K+ channels, leading to arteriolar vasodilation. In MS, astrocytes are
K+ released during action potential propagation at the nodes of Ranvier enters astrocytes through Kir, especially
Kir4.1. K+ is intracellularly redistributed to restore a correct ionic balance at the nodes of Ranvier, and released into
K+ transport
Figure 2: Possible brain microcirculatory dysfunction in MS white matter resulting from impaired astrocytic
K+ transport. K+ released during action potential propagation at the nodes of Ranvier enters astrocytes through Kir, especially
Kir4.1. K+ is intracellularly redistributed to restore a correct ionic balance at the nodes of Ranvier, and released into
the perivascular space through Ca²+-activated K+ channels, leading to arteriolar vasodilation. In MS, astrocytes are
deficient in β2-adrenergic receptors (1), which stimulate glycogenolysis, and have reduced phosphocreatine
metabolism caused by decreased CK-B activity (2). The resultant decreased astrocytic energy metabolism might
lead to reduced astrocytic K+ uptake and subsequent release in the perivascular space, leading to reduced arteriolar
vasodilation (shown in red). MS=multiple sclerosis. Kir=inwards rectifying K+ channel. cAMP=cyclic adenosine
monophosphate. PCr=phosphocreatine. Cs=creatine. CK-B=creatine kinase B. ADP=adenosine diphosphate. ATP=adenosine triphosphate.

Relevance of brain hypoperfusion in MS
An important but unresolved question is whether reduced cerebral perfusion in MS contributes to an
increased risk of developing ischaemic stroke. There are substantial similarities in histopathological changes
between focal MS white matter lesions and classic ischaemic white matter disease, particularly in type 3
focal MS lesions (which were defined by a group of neuropathologists).64

In a study that compared gene expression in the NAWM of patients with secondary progressive MS with that of
healthy control individuals, one of the most consistent differences was enhanced expression of hypoxia-inducible
factor (HIF)-1α and its downstream genes in patients with MS.65 HIF-1α is a transcription factor that transactivates
genes encoding proteins that participate in homeostatic responses to hypoxia.65 A similar upregulation of HIF-1α
has been found in the cerebral white matter of patients with ischaemic leukoencephalopathy.66 Additionally,
oligodendrocytes in focal MS lesions express high concentrations of p53,66 which is a stress protein that
becomes activated in ischaemic brain regions.66

Binswanger’s chronic ischaemic leukoencephalopathy is a prototypical disease of reduced CBF in white matter,67
and represents a common cause of cognitive impairment. Cognitive manifestations in individuals with MS are
similar to those in Binswanger’s chronic ischaemic leukoencephalopathy.67 A direct relation has been
described between deep grey matter and NAWM perfusion changes and cognitive decline in patients with
relapsing-remitting MS and primary progressive MS.68

Venous blood drainage in MS
Cerebral venous drainage
The cerebral venous system is often asymmetrical and is
characterised by a substantially more variable pattern
than the arterial anatomy.69 Basically, venous blood is
collected in cerebral veins and dural sinuses and then
directed towards the main extracranial evacuating
routes—ie, the internal jugular veins and the vertebral
veins. Both systems terminate in the brachiocephalic
vein. The vertebral system is also responsible for spinal
column drainage and communicates with the lumbar
and azygos-hemiazygos veins.

Posture and mechanical movements of respiration play
a fundamental part in ensuring correct cerebral venous
outflow. Inspiration causes contraction of the diaphragm
and respiratory muscles. This contraction leads to a more
negative intrathoracic pressure and facilitates venous
return to the heart. The internal jugular veins are the
predominant extracranial outflow pathways in the supine
position. Redirection of venous blood flow towards the
vertebral veins occurs in the upright position.6971

The concept of CCSVI
Zamboni and colleagues69,72 recently described an
association between MS and a condition defined as

Panell: Transcranial and extracranial colour-doppler
high-resolution venous haemodynamic criteria for chronic
cerebrospinal venous insufficiency69
• Reflexus constantly present in the internal jugular veins or
vertebral veins, or both, with the head at 0° and +90°
• Reflexus in the deep cerebral veins
• High-resolution B-mode evidence of proximal internal
jugular vein stenoses
• On doppler imaging, flow not detectable in the internal
jugular veins or vertebral veins, or both, despite numerous
depth inspirations with the head at 0° and +90°
• Negative change in cross-sectional area in the internal
jugular vein

pump, which is key in establishing the negative membrane
potential necessary for optimum intracellular K+
redistribution and Kir function.63 Thus, the reduced
energy production in astrocytes in patients with MS
might result in lower K+ recovery in the perivascular space
and a reduced state of arteriolar vasodilation (figure 2).

Increased blood concentrations of the vasoconstrictive
compound endothelin-1 (ET-1) in patients with MS might
also contribute to the widespread cerebral hypoperfusion.64 65 Pache and colleagues69 noted reduced blood
flow velocities in extracapillary vessels of patients with MS
who had raised ET-1 blood concentrations.

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The concept of CCSVI
Zamboni and colleagues69,72 recently described an
association between MS and a condition defined as
CCSVI, which is characterised by a high incidence of reflux in both intracranial and extracranial venous segments, loss of postural venous outflow regulation, the presence of multiple stenoses of unknown origin in the internal jugular veins and azygos vein, and the opening of collateral circles. This concept has had an impressive effect on the MS community.

In the original description of the association, combined extracranial high-resolution echo-colour doppler (ECD) and transcranial colour-coded doppler sonography (TCDS) were used as non-invasive methods to detect CCSVI in 65 patients with MS and 235 control individuals.72 The team focused in particular on the detection of five abnormal venous haemodynamic parameters (panel). The CCSVI diagnosis needed to fulfil at least two of these five parameters. The detection of two or more parameters in the same patient was not found in any of the healthy controls or patients with other neurological disorders, but perfectly overlapped with the diagnosis of clinically definite MS, in terms of a reported 100% sensitivity, specificity, positive predictive value, and negative predictive value. The ECD-TCDS findings in this study were verified by transfemoral selective venography, which also showed a significantly higher pressure gradient across the venous stenoses.72

Venous stenoses in the main cerebrospinal outflow routes were never isolated in patients with MS, and four different patterns of distribution, named A, B, C, and D, were defined (table 1). Primary progressive MS was mainly associated with the type D pattern and relapsing-remitting MS was particularly associated with type A mainly associated with the type D pattern and relapsing-were defined (table 1). Primary progressive MS was mainly associated with the type D pattern and relapsing-remitting MS was particularly associated with type A and B patterns.72,74 These findings led to the hypothesis that the location of venous obstructions might influence the clinical course of MS. This variability in CCSVI presentation was postulated to have a specific genetic background.72

Two independent groups who used the same methodology and terminology have published similar data supporting an association between CCSVI and MS. Simka and colleagues77 assessed the extracranial doppler sonographic criteria for CCSVI in 70 patients with different clinical forms of MS. Signs of abnormal venous outflow were noted in 64 (91%) patients with MS and 63 (90%) fulfilled the criteria for CCSVI. The most common pathological sign was the presence of an inverted valve or another pathological structure, such as a membranous or netlike septum, in the junction between the internal jugular and brachiocephalic veins.77 Al-Omari and Rousan77 reported that 23 of 25 (92%) patients with MS and six of 25 (24%) control individuals had abnormal extracranial internal jugular vein findings. CCSVI criteria were met in 21 (84%) patients with MS and none of the control individuals. Furthermore, a membranous or netlike septum, in the junction between the internal jugular and brachiocephalic veins.77 Al-Omari and Rousan77 reported that 23 of 25 (92%) patients with MS and six of 25 (24%) control individuals had abnormal extracranial internal jugular vein findings. CCSVI criteria were met in 21 (84%) patients with MS and none of the control individuals. Furthermore, a recent transcranial and extracranial ECD study by Zivadinov and colleagues78 also showed a significantly increased prevalence of CCSVI in patients with MS (62-5%) compared with healthy control individuals (25-5%) but with substantially lower sensitivity and specificity rates than originally reported.

However, several other sonographic studies have been unable to replicate the findings of Zamboni and colleagues (table 2).73-81 Doep and co-workers79 did an extended ECD and TCDS study that included analyses of extracranial venous blood volume flow, cross-sectional areas, internal jugular vein flow during the Valsalva manoeuvre, and CCSVI criteria in 56 patients with MS and 20 control individuals. Except for one patient with MS, blood flow direction in the internal jugular veins and vertebral veins was normal, and none of the patients had internal jugular vein stenosis. Internal jugular vein and vertebral vein blood volume were equal in the supine position in both groups. No differences between the two groups were noted in intracranial veins or during the Valsalva manoeuvre. None of the patients investigated in this study fulfilled more than one criterion for CCSVI. Venous drainage via the internal jugular veins in the upright position was higher in patients with MS than in control individuals, which is an interesting but unexplained finding. Beggs80 proposed that this difference in venous drainage might suggest that a greater proportion of venous blood from the brain flowed through the internal jugular veins because of stenoses in extrajugular venous pathways, but the Doep team81 replied that this was not the case. Mayer and colleagues80 examined the extracranial and intracranial venous blood flow direction with colour-coded doppler sonography and the extracranial venous cross-sectional area of the internal jugular veins and vertebral veins in B-mode sonography to assess whether the five previously proposed CCSVI criteria were met in 20 patients with MS and 20 healthy control individuals. No participant had retrograde flow of extracranial or intracranial veins. Evidence of internal jugular vein stenosis was noted in 13 patients with MS and 16 control individuals. No patient with MS and one healthy control fulfilled at least two criteria for CCSVI. Both studies79,81 were limited by the small sample sizes, but benefited from an excellent and reproducible doppler methodology, which included a masking procedure in the latter study.81 The discrepancies between the positive

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Type A 20%</td>
<td>Steno-obstruction of the proximal azygos vein, associated with obstruction of one of the two internal jugular veins</td>
</tr>
<tr>
<td>Type B 38%</td>
<td>Significant stenosis of both internal jugular veins, as well as the proximal azygos vein</td>
</tr>
<tr>
<td>Type C 14%</td>
<td>Bilateral stenosis of the internal jugular vein, with a normal azygos vein</td>
</tr>
<tr>
<td>Type D 18%</td>
<td>Multilevel involvement of the azygos vein and lumbar systems, with or without involvement of the internal jugular vein</td>
</tr>
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</table>

Table 1: Patterns of venous stenosis distribution in chronic cerebrospinal venous insufficiency72,74
and negative studies on CCSVI might be explained by methodological differences in examining venous CBF, which is technologically more complex than the assessment of arterial blood flow.

A novel phase-contrast MRI technique that allows better visualisation of the cerebral veins was used by Sundström and colleagues⁸⁴ to investigate 21 patients with relapsing-remitting MS and 20 healthy control individuals. No differences were found between groups in internal jugular venous outflow, aqueductal CSF flow, or the presence of internal jugular venous reflux. Patients with MS underwent additional MRI venography, but only three of 21 had internal jugular venous stenosis. In a three-dimensional phase-contrast and DSC-MRI venography study of intracranial and neck veins, there was a similar frequency of stenosing anomalies in 20 patients with MS and 20 age-matched and gender-matched control individuals.⁸⁵ Flow quantification of the internal cerebral veins and the straight sinus was included, but did not show venous back flow in any of the participants. Given normal flow quantification results, the findings, which were suggestive of structural venous outflow anomalies, were interpreted as anatomical variants without pathological significance. A recent MRI venography study of the extracranial veins draining blood from the brain failed to find morphological differences between 57 patients with MS and 21 healthy control individuals.⁸⁵ Although this imaging technique possibly had lower sensitivity than ECD-TCDS, these MRI results cast further doubt on the existence of relevant structural venous outflow abnormalities as a pathological entity in MS.

Possible mechanisms linking CCSVI and MS

Because of the perivenular pattern of focal MS lesions, CCSVI was suggested to stretch venous walls and separate endothelial tight junctions, leading to extravasation and degradation of erythrocytes, resulting in iron deposition surrounding the veins in the CNS parenchyma.⁸⁶ Although iron is essential for normal CNS physiology, its redox switching capacity also makes it a proinflammatory chemotactic substance that could contribute to or worsen lesion formation in MS.⁸⁷,⁸⁸ Using susceptibility-weighted MRI, Haacke and colleagues⁸⁹ found that patients with MS had above normal iron concentrations in the thalamus and basal ganglia, with a deposition pattern that was particularly associated with venous drainage routes. Raised iron concentrations in the thalamus, globus pallidus, and hippocampus were associated with a higher number of ECD-TCDS-detected CCSVI criteria, longer disease duration, increased disability, increased MRI lesion burden, and decreased brain volume.⁹²

The theory that venous stasis leads to perivenular iron deposition that in turn causes focal inflammatory demyelinating lesions might not be correct for several reasons. First, inflammatory lesions in experimental allergic encephalomyelitis (EAE) are also distributed around small veins. EAE is a pure autoimmune animal model of inflammatory demyelinating responses in the CNS that is induced by injecting proteins that make up myelin without any evidence of venous stasis. Rather, the cause of the venous distribution of lesions is probably the slowness of blood flow (due to a higher resistance in the capillary branches) at these sites compared with the remainder of the cerebral vasculature.⁹³ In the postcapillary venules, this slowness of blood flow provides locally activated anti-myelin T cells with maximum opportunity for interaction with the endothelial surface, and thus these T cells can readily pass through the endothelial layer and enter the perivenular white matter without difficulty.⁹⁴ Activated anti-myelin T cells entering the perivenular white matter might initiate local inflammation and lesion formation. Abnormal iron deposits are present not only in MS lesions but also in EAE lesions.⁹⁵ Oligodendrocytes normally have high iron concentrations, probably because of increased expression of enzymes involved in myelin production. The high iron concentrations in MS and EAE lesions might be caused by the release of iron

**Table 2: Venous outflow abnormalities as measured with doppler sonography in patients with multiple sclerosis and control individuals.**

<table>
<thead>
<tr>
<th>Criterion 1</th>
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<td>Baracchini et al⁸⁶</td>
<td>12/50*</td>
<td>0/50</td>
<td>0.0002</td>
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<td>NS</td>
<td>8/50*</td>
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<td>0.005</td>
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<td>NS</td>
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Criteria 1-5 of chronic cerebrospinal venous insufficiency are explained in the panel. NS = not significant. *Patients with clinically isolated syndromes.
from the proteins to which it normally binds as a result of oligodendrocyte destruction, which occurs during inflammatory lesion formation in both MS and EAE. Other possible mechanisms include blood–brain barrier disruption, accumulation of iron-rich macrophages, and reduced axonal clearance of iron.69,70 Thus, iron overload in the CNS of patients with MS might be secondary to inflammation and not the reverse. Second, CNS iron accumulation frequently occurs in other neurodegenerative disorders, such as Parkinson’s disease and Alzheimer’s disease,7 without causing demyelination, and patients with impaired venous cerebral outflow, such as venous sinus thrombosis, do not have increased prevalence of MS.68 Third, a study that used ECD-TCDS found no significant differences in CCSVI occurrence between patients with a clinically isolated syndrome suggestive of MS and control individuals.67 Although criteria 1 and 3 were significantly different between the two groups, this was not sufficient to diagnose CCSVI, which requires at least two positive criteria in each person. All patients who fulfilled the CCSVI diagnosis had normal selective venography results. These results strongly suggest that CCSVI is not a causative factor in early MS. Additionally, in a study in which selective venous angiography was done in 42 patients with MS, extracranial venous stenoses were rare in early MS (seven of 29 patients) but became more common in patients with disease duration of more than 10 years (12 of 13), suggesting that some stenoses in the brain outflow veins might be a secondary phenomenon in MS.69 The high re-stenosis rate after endovascular CCSVI dilatation treatment might also add support to this hypothesis.100 Also, pathological changes in MS are possibly associated with a release of inflammatory cytokines or vasoactive substances, such as ET-1, which might have a vasoconstrictive action on the venous wall that possibly contributes to the development of stenosis.

Zamboni and colleagues101 recently described a significant association between the severity of CCSVI and reduced CBF in the brain, suggesting that the cerebral hypoperfusion in MS might be caused by venous outflow obstructions. However, an experimentally induced increase in cerebral venous pressure does not lead to reduced CBF unless the pressure is increased up to the systolic blood pressure level,101,102 which is non-physiological and does not occur in MS. Conversely, reduced CBF is associated with decreased venous flow.10 Thus, slower blood flow through the cerebral veins might be the consequence of reduced arterial blood flow rather than being caused by venous outflow obstructions, and might eventually explain findings of CCSVI in some patients with MS. High-field susceptibility-weighted MRI, in which the cerebral veins are directly imaged by exploiting venous blood oxygenation, showed a markedly reduced visibility of periventricular white matter venous vasculature in patients with MS compared with control individuals.104 This reduction might point to a decreased level of oxygen extraction caused by reduced cerebral perfusion. Venous stasis, which forms the basis of the theory put forward by Zamboni, would be expected to contribute to the enhancement of susceptibility effects, resulting in greater visibility of venous structures because of increased oxygen extraction from vessels experiencing reduced evacuation of blood.

**Endovascular interventions**

The concept of CCSVI has received much attention in the MS community. Neurological improvement, including reduced relapse rate, reduced disability, and better quality of life, was reported in two small prospective uncontrolled cohorts of patients with MS who had percutaneous endovascular dilatation treatment of venous stenoses for CCSVI.100,105 Many patients actively seek centres where percutaneous endovascular dilatation treatments are done, and more and more vascular surgeons or interventional radiologists are offering this mode of treatment. On the internet, many patients report benefits from this intervention, which is often referred to as the “liberation procedure”. However, there is an urgent need for rigorously controlled studies of this treatment. The available evidence does not support the theory that CCSVI is a cause of MS, and CNS venous outflow studies suggest that there is great variability in anatomical variants in patients with MS and in healthy control individuals. Although a short-lasting placebo effect might explain the success stories reported by patients after the endovascular procedure, we cannot exclude the possibility that the endovascular interventions provoke biochemical changes that might temporarily improve MS symptoms. Until more scientific data are available, we endorse the Cardiovascular and Interventional Radiological Society of Europe guidelines,106 which formally state that endovascular dilatation treatment for jugular vein stenoses in patients with MS should not be undertaken outside well designed clinical trials.

**Conclusions**

In this Review, we have outlined three forms of vascular abnormalities that have been described in MS. Patients with MS seem to have an increased risk for ischaemic stroke. Endothelial dysfunction secondary to inflammatory responses or raised homocysteine concentrations might play a part, but reduced CBF might predispose patients to the development of these ischaemic brain lesions. The widespread cerebral hypoperfusion in MS seems not to be secondary to axonal degeneration, but might be a result of reduced axonal activity, reduced astrocyte energy metabolism, and perhaps increased blood concentrations of ET-1. Impaired cerebral perfusion seems to be especially related to cognitive manifestations of the disease, which is a common symptom associated with substantial decline in activities...
of daily living. Investigation of whether interventions that improve cerebral perfusion improve cognitive function in patients with MS would be of interest. Statements that suggest that insufficient cerebral venous drainage might play a causative part in MS have shaken both the medical and patient community. Although there is no compelling evidence to suggest that CCSVI is a cause of MS, there are some suggestions of a slower cerebral venous flow in patients with MS, which might be secondary to the reduced CBF. There is at present no evidence for a cerebral venous outflow obstruction or stasis in MS, and endovascular procedures for jugular vein stenoses should be undertaken only in well controlled clinical trials.

Contributors
MD wrote the first draft, and MC, LV, and JDK were involved in writing, critical review, and revision of the manuscript.

Conflicts of interest
LV has received travel support and lecture fees from Merck Serono, and fees for board membership from UCB, Bayer Schering, Biogen Idec, Novartis, and Teva; institutional grant support from Merck Serono; and fees for board membership from UCB, Bayer Schering, Biogen Idec, Novartis, and Teva. MD, MC, and JDK declare that they have no conflicts of interest.

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Search strategy and selection criteria
References for this Review were identified by searching PubMed (from 1954, to April, 2011) for various combinations of the search terms “multiple sclerosis”, “vascular disease”, “cardiovascular disease”, “atherosclerosis”, “endothelial dysfunction”, “homocysteine”, “cerebral perfusion”, “normal appearing white matter”, “endothelin-1”, “chronic cerebrospinal venous insufficiency”, and “venous drainage”. The reference lists of recent articles were additionally screened as were the authors’ own files to find other previously unidentified articles. All except one reviewed paper were published in English.
Review


