Chronic cerebrospinal venous insufficiency in multiple sclerosis: a historical perspective

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Summary

Chronic cerebrospinal venous insufficiency (CCSVI) is a term used to describe impaired venous drainage from the central nervous system (CNS) caused by abnormalities in anatomy and flow affecting the extracranial veins. Recently, it has been proposed that CCSVI may contribute to the pathogenesis of multiple sclerosis (MS). It is hypothesized that venous obstruction results in abnormal flow that promotes inflammation at the blood-brain barrier and that this triggers a process marked by a disturbance of homeostasis within the CNS that leads to demyelination and neurodegeneration. The venous abnormalities of CCSVI are often diagnosed by ultrasound or magnetic resonance venography, however the prevalence of CCSVI detailed in groups of MS patients and patients without MS varies widely in published reports. Increased standardization of diagnostic studies to evaluate both anatomical and physiological findings associated with CCSVI is needed. The purpose of this article is to provide a background to understand the development of the theory of CCSVI and to frame the relevant issues regarding its diagnosis and relationship to the pathogenesis of MS.

KEY WORDS: association, blood-brain barrier, chronic cerebrospinal venous insufficiency, demyelination, diagnosis, multiple sclerosis, pathogenesis, vascular

Historical perspective

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease that affects the central nervous system (CNS). It is estimated that it currently affects 400,000 individuals in the U.S. and with 12,000 new cases annually, more people are being diagnosed now than in the past. It is a disease with disseminated brain and spinal cord lesions, a wide variety of different neurological symptoms, and typically a fluctuating clinical course. The symptoms of this multicentric process are manifest during acute relapses of the disease or after a period of disease progression. While the clinical course of MS is highly variable, in most cases it leads to severe and irreversible disability (1-3).

Recognized and described over 150 years ago, the exact cause of MS remains unknown. Credit for the first complete clinical and pathological account of MS is attributable to Charcot, the renowned French neurologist (4). He first became familiar with the progress of the disease through daily observation of his housemaid, who had nystagmus, intention tremor, and scanning speech. He used freehand cut brain sections and primitive methods of staining in a number of cadaver brains to identify the salient histopathological features of the disease and emphasized the loss of myelin sheaths, the preservation of nerve fibers, and the proliferation of glia.

It is now generally held that an autoimmune mechanism is responsible for the disease, but how the initial reaction is triggered and the process sustained remains unclear. Multiple factors (genetic, infectious, environmental, nutritional, etc.) have been implicated in the etiology of MS and an interaction between various factors could potentially explain the heterogeneity observed in studies of both the pathological character of MS lesions and the nature of disease manifestations. To date, no single factor is known to be causal (2,3).

Chronic cerebrospinal venous insufficiency (CCSVI) is a recently described condition that may possibly contribute to the symptoms often experienced by patients with MS (5,6). The idea that the vascular system is somehow related to the pathological abnormalities of MS was proposed shortly after the characteristic lesions were described. Of the early investigators of the disease, Charcot was the first to describe the obstruction of blood vessels within MS lesions (4). Indeed, the vascular hypothesis was widely advocated as the most plausible explanation for the pathogenesis of MS during the late 1800s.

Observations by Rindfleisch and others detailed blood vessels within the middle of each white matter lesion (7,8). In 1863, Rindfleisch wrote, “if one looks carefully at freshly altered pats of the white matter, one perceives already with the naked eye a red point or line in the middle of each individual focus, the lumen of a small vessel engorged with blood. All this leads us to search for the primary cause of the disease in an alteration of individual vessels and their ramifications.”

Then, during the mid-20th century, the recognition that these central vascular channels were abnormal cerebral veins fueled enthusiasm for the concept of a vascular etiology. During this period, researchers including Putnam, Marburg, Dow, Fog, Adams, Engell and others

(9-23) contributed to advancing an understanding of the role of abnormal venous involvement in MS, but over the last 50 years the vascular hypothesis has been eclipsed by emerging evidence that strongly supports a primary autoimmune basis for the disease.

Chronic cerebrospinal venous insufficency

Recently, Zamboni and colleagues revitalized interest in the importance of cerebrospinal venous drainage as a factor that influences the pathogenesis of MS (6,24,25). They described ultrasonographic and venographic evidence of extracranial venous obstruction involving the internal jugular, vertebral, deep cerebral and azygos veins in a remarkably high percentage of patients diagnosed with MS. Comparatively, similar findings were not diagnosed in healthy control subjects and patients with other neurological diseases. They proposed that CCSVI interferes with venous drainage from the CNS, and that this contributes to the development and progression of MS. Moreover, when the stenotic lesions in the internal jugular and azygo veins were treated endovascularly with balloon angioplasty, they observed in many patients a rapid and often dramatic improvement in a variety of symptoms (25). This approach was in fact not dissimilar to that taken in treating paraplegic and quadriplegic patients in the 1970s by Aboulker et al. (26,27). During this time, Aboulker and colleagues treated hundreds of patients and pioneered the pathogenetic concept of venous hypertension as primarily responsible for the neurological abnormalities. They documented lesions not only in the jugular and azygos veins, but also in the brachiocephalic, superior vena cava and iliac veins.

Zamboni and co-authors detailed the non-invasive detection of CCSVI by combined transcranial and extracranial color Doppler ultrasonography. This specific examination included the evaluation of five parameters to assess venous blood flow and anatomy (6,24). The study was considered diagnostic of CCSVI if a patient had an abnormality in two or more of the five criteria studied. The diagnosis of CCSVI by these investigators was highly associated with all forms of MS, irrespective of the relapsing-remitting or progressive nature of the disease in the group of patients tested. They hypothesized that the venous abnormalities identified are responsible for derangements in the normal patterns of blood flow draining from the CNS and consequently cause inflammatory reactions at the blood-brain barrier that lead to altered permeability and a cascade of untoward changes including iron deposition, degeneration of neurons and characteristic forms of brain injury typical of MS (5,28).

The publication of these findings unleashed an emotionally intense controversy that currently still foments with boiling points of view. From highly critical reactions that decry the concept of CCSVI as a hoax that provides false hope to vulnerable and desperate individuals to supportive testimonials from treated patients, the debate surrounding the existence, association and relevance of CCSVI to MS is reflected in the contributions to the medical literature. Although the vast majority of the articles on the topic consist of commentaries, opinions, interpretations and diatribes rather than reports of clinical evidence for or against CCSVI, the essence of the recently published independent clinical studies designed to evaluate various aspects of the CCSVI hypothesis do, by and large, reflect the opposing public contentions in the dispute by presenting conflicting results that either pointedly question or support the existence of CCSVI (29-33). At present, our level of understanding is simply insufficient to settle the argument (34,35).

Many of the reports in the literature have focused on corroborating the ultrasound results initially published by Zamboni. Some authors presented findings that did not confirm an increased frequency of venous abnormalities in MS patients relative to healthy control subjects or patients with other neurological diseases, while others found positive CCSVI ultrasound criteria more commonly in MS patients compared to controls (36-38). Other studies have evaluated MR venography, MR determinations of jugular venous flow, brain perfusion, iron content and MR evaluations of intracerebral total venous volume in patients with and without diagnosed CCSVI, as well as traditional catheter venography, ultrasonography, and functional MR studies before and after endovascular treatment of patients with CCSVI (39-44). Despite these independent single center efforts, it will require another level of controlled, collaborative multimodal research with agreement on clear definitions of standards for CCSVI testing, interpretation, and diagnosis before the confusion can be resolved (29,34).

Pathogenesis of MS in relation to venous alterations

In recognition of our current inability to fully understand the role, if any, of CCSVI and its relevance to the pathogenesis of MS (34,35), other neurological diseases or healthy subjects, it may be interesting to review some of the historical pre-CCSVI evidence that supports the functional influence of venous involvement and its possible importance to the pathogenesis of MS. In this regard, these contributions provide the foundational underpinning for the current CCSVI theory. Perhaps, one of the more interesting areas of observational research involves the similar appearances of veins that are subjected to chronic obstruction in a variety of venous territories throughout the body (Fig. 1). Histopathological examination of leg veins from patients with chronic lower extremity deep venous thrombosis, hepatic veins in patients with Budd-Chiari, and retinal veins in patients with chronic forms of optic neuritis show the same response that has been observed in cerebral veins located within the brain lesions in MS patients (45,46).

Regardless of the location of the involved vascular bed, veins that are exposed to chronic downstream obstruction respond to the associated sustained increase in pressure (even though it may be only modestly elevated over normal at rest) and flow disturbances in a characteristic manner by forming a “fibrin cuff” that encircles a typically dilated vessel lumen as a proliferative thickened wall consisting of concentric lamellae of hyaline material that replaces the normal lacy perivenous connective tissue (Fig. 2) (5,28). This interesting adaptive structural reaction to venous insufficiency is similar throughout the body, irrespective of the etiology or location of the venous obstruction. In relation to MS, the effects of this venous involvement and its relationship to the pathogene-

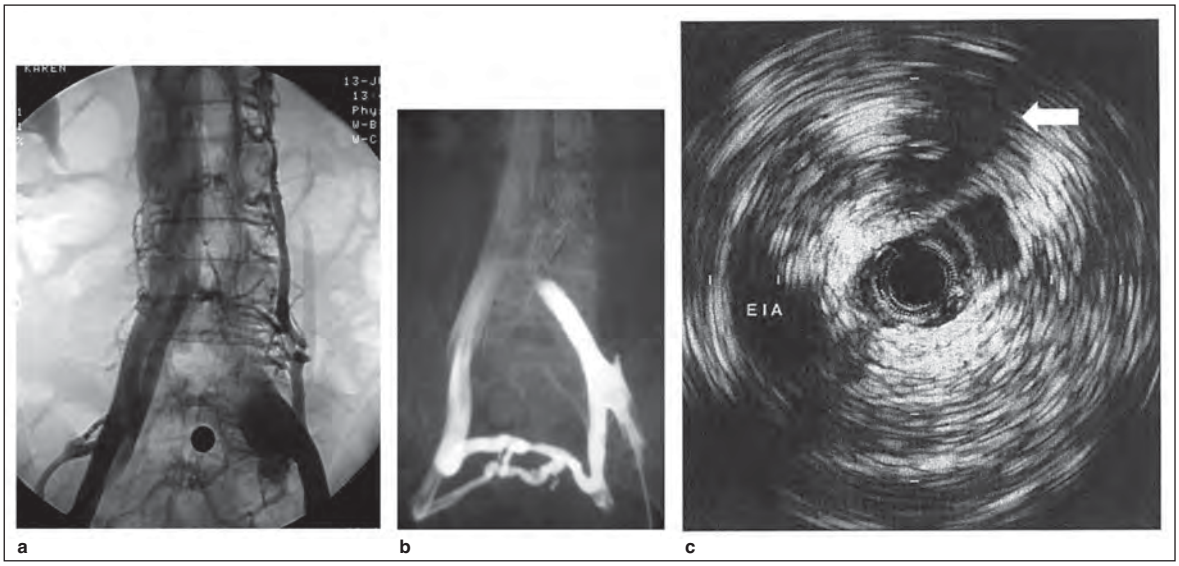


Figure 1 - Venous obstruction due to extrinsic compression of the left common iliac vein.
(a) Left iliac venogram with compression of left common iliac vein caused by overlying right common iliac artery as it crosses anterior to the vein. Posteriorly, the spine prevents displacement of the vein. This is typical of the May-Thurner syndrome with left common iliac vein obstruction. The narrowing is seen as a diagonal effacement of the contrast column coursing across the vein from upper left to lower right, corresponding to an extrinsic compression from the right common iliac artery. (b) Similar venographic appearance of the left common iliac vein in an older individual with asymmetric left leg swelling. Note the calcified aorta and right iliac artery that allow appreciation of the relationship between the crossing artery and the obstructed left common iliac vein. Also evident are numerous transpelvic venous collaterals that provide flow around the obstruction. (c) Intravascular ultrasound image with catheter located in the left iliac vein. The vein is markedly narrowed by the overlying iliac artery that is located anteriorly at 12 o'clock (arrow).

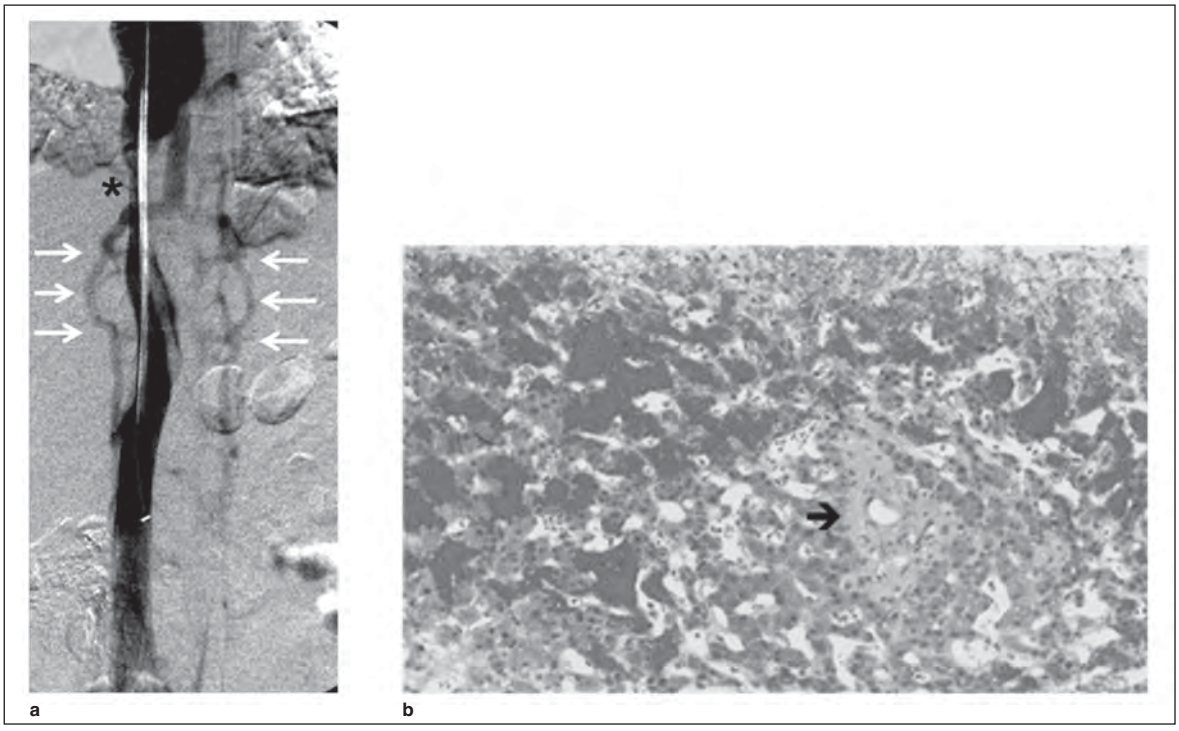


Figure 2 - Budd-Chiari syndrome with chronic venous obstruction.
(a) Inferior vena cavogram with intrahepatic stenosis (asterisk) associated with multiple collateral channels (arrows) in 30-year-old woman with history of oral contraceptive use and symptoms of abdominal pain and swelling. (b) Photomicrograph of a transjugular liver biopsy specimen in this patient with findings typical of Budd-Chiari syndrome. Thickened hepatic vein wall (arrow) is noted with proliferative changes comprising a hyalinized fibrin cuff around the chronically obstructed vein. Also evident is perivenular congestion with clustering of red blood cells. (original magnification, x40; hematoxylin-eosin stain)

sis of the CNS involvement have been explored for decades as an unexplained curiosity in an unexpected academic venue—the ophthalmology literature.

Optic neuritis is recognized as one of the most common first manifestations of MS. It is estimated that 66% of MS patients will have at least one episode of optic neuritis (47,48). The symptoms of optic neuritis or retrobulbar neuritis usually include acute blurring or loss of vision that typically involves one eye. Not everyone who experiences optic neuritis develops MS. Over a 10-year period after an episode of optic neuritis, it is estimated that about 40% of individuals will be diagnosed with MS (49). While not every case of optic neuritis is associated with MS, C. Wilbur Rucker, an ophthalmologist at the Mayo Clinic, described, over 60 years ago, in 1944, a "peculiar white sheathing of some of the retinal veins" observed on fundoscopic examination of MS patients (47,48). This retinal vein sheathing "appears as a thickening of the walls of the veins, especially in their peripheral branches, and there occasionally may be constriction in caliber of the lumen." Further studies by Rucker and others revealed that this phenomenon is detected in about 10% to 23% of patients with MS; furthermore, when it is documented, the vast majority of the affected patients (85% to 90%) have or eventually progress to a diagnosis of MS (50,51).

In 1976, Younge performed fluorescein angiographic observations in a group of patients with retinal vein sheathing and MS (52). He reported "smudge-like" fluorescein staining of the vein wall 15 minutes after the dye was administered and leakage spreading into the region of sheathing at 30 minutes. He believed the breakdown in the blood-retinal barrier to be a form of perivasculitis that represented a contributing factor in the sheathing process. Interestingly, Broman, working in Lund in 1947, described similar staining with a supravital dye within the white matter plaques in two cases of MS (53). The disturbed cerebral vascular venous permeability he observed most notably occurred within the lesions at vessel branch points. Hamrick and King recounted in the ophthalmology literature that one of the early theories regarding the retinal venous phenomenon, regardless of its cause, was that it "might be the underlying lesion producing the clinical disease of multiple sclerosis," and "thus it has been postulated that a mild form of localized phlebitis may be responsible for the demyelinating process" (54).

Subsequently, Lightman, et al., in 1984 published a "systematic study" of the frequency of retinal vascular abnormalities in 50 patients presenting with acute optic neuritis (55). None of the patients had a diagnosis of MS at the time of initial examination and enrollment in the study. Abnormalities were detected in 14 of the patients with optic neuritis, including 10 cases of fluorescein leakage and 6 cases of perivenous sheathing. After a mean follow up of 3.5 years, MS had developed in 8 of the 14 patients with vascular abnormalities (57%). This represented a statistically significant difference ($p<0.02$) in the occurrence of MS compared to the patients without vascular lesions diagnosed. He concluded that, "The presence of perivenular abnormalities in a region free of myelin and oligodendrocytes provides evidence that the vascular changes in MS can occur independently of contiguous demyelination, and may be the primary event in the formation of new lesions"(55).

Allen observed that the perivascular cuffing in the retina in optic neuritis and MS occurs in a region which is free of myelin and oligodendrocytes which cannot therefore be necessary for the initiation of the cellular infiltration and vascular changes (56). Lightman then strongly argued against the view that "the vascular changes in MS are secondary to myelin breakdown produced in some other way" and focused attention on the possibility that "the primary events leading to demyelination occur at the vascular endothelium" (55). In a 1987 publication, Shaw stressed the "importance of retinal periphlebitis in MS in increasing our understanding of the pathogenesis of demyelinating plaques in the central nervous system" and proceeded to be the first to describe the histopathology of the retinal lesion in detail (57).

In his discussion, Shaw (57) noted that Adams (20) had previously suggested that perivenular inflammatory cell cuffing in the CNS may be the first event in plaque formation. Fog (17) and others (58,59) had also argued that the occurrence of periphlebitis retinae favors the hypothesis that vascular changes are the primary factor in the genesis of MS plaques. Shaw reported that if the "findings of the present study are combined with the previously reported histological studies (of cerebral MS lesions), a picture emerges of the active and chronic stages of periphlebitis retinae associated with multiple sclerosis. In the active phase the vascular changes resemble those around vessels in the acute phase of CNS plaque formation. In many chronic CNS plaques, blood vessels have thick collagenous walls. These appearances are similar to the findings we describe in the case of chronic periphlebitis retinae. Such histological similarity between the vascular changes in CNS plaques and retinal periphlebitic lesions suggests that they may have a common pathogenesis. Periphlebitis may therefore be an initial event in plaque formation, as has been suggested by several other authors. If this is the case, periphlebitis retinae may represent the basic lesion of MS in a clinically visible site" (57).

So, if a perivenulitis involving segments of the cerebrospinal blood-brain barrier is a component of the pathogenetic process in MS and myelin and/or myelin-related proteins are not inciting factors requisite for the process, what is causing the reaction? The truth is, it is still not known what triggers the initial events in MS. Most scientists believe that a combination of several factors may be involved. In this context, CCSVI may represent one of these contributing factors (35). As such, it is of interest to review some of the existing evidence that supports the hypothetical rationale for CCSVI involvement in MS. As mentioned in a recent review, perhaps it is time to consider the concept of "vascular immunology" as a focus in understanding the immunological effects of disrupting the vascular system (35).

Overview of diagnostic issues in relation to CCSVI

As previously discussed, the venous stenoses described in CCSVI involve predominantly the internal jugular and azygos veins, but in theory because it is the existence of venous obstruction that is important, rather than its precise location, the narrowing of other veins draining the cerebrospinal axis may play a role. These may include intracranial channels such as major intrac-

erebral veins, ophthalmic veins, petrosal sinuses and dural sinuses, as well as extracranial vessels including the vertebral veins, left brachiocephalic vein or normally existing collateral neck veins (25). In terms of venous insufficiency affecting the more commonly involved internal jugular and azygos veins, the presence of multiple lesions affecting one or more veins is frequently observed in CCSVI. Present experience with endovascular treatment of CCSVI consistently details a mean number of lesions detected in a range of 1.6 to 1.8 stenoses per patient evaluated (25,60-62).

The exact location of the internal jugular lesions observed is variable. Similarly, the cause of venous narrowing at any level may be different, with detection of both intrinsic vein abnormalities and extrinsic compression which may be a dynamic or fixed obstruction. In this regard, however, some more commonly identified patterns of venous obstruction have emerged. By far the most frequently identified site of venous abnormalities is at the region of the jugular valve just cephalad to the internal jugular confluence with the brachiocephalic veins on either side, but narrowing within the high and mid-cervical segments of the internal jugular vein have also been recognized (40,41,43,60-63).

The high internal jugular stenoses are commonly associated with displacement and compression of the vein as it courses over the anterior aspect of the lateral mass of the C1 vertebral body (Fig. 3). As the internal jugular vein (sigmoid sinus) exits the skull and becomes the jugular bulb, it is directed anteriorly to sweep over the lateral arch of the first cervical vertebra. The angle the vessel must assume as it passes from the jugular foramen to its position in front of the bone is variable depending on an individual's anatomical structure and any distortion of the vein associated with its position at this level may be accentuated or reduced by a variety of orientations of the head and neck. Supine or prone posture, flexion or extension of the neck, ipsilateral or contralateral rotation of the head, as well as maneuvers that combine these positions may all influence the degree of any stretching of the internal jugular and resultant venous obstruction.

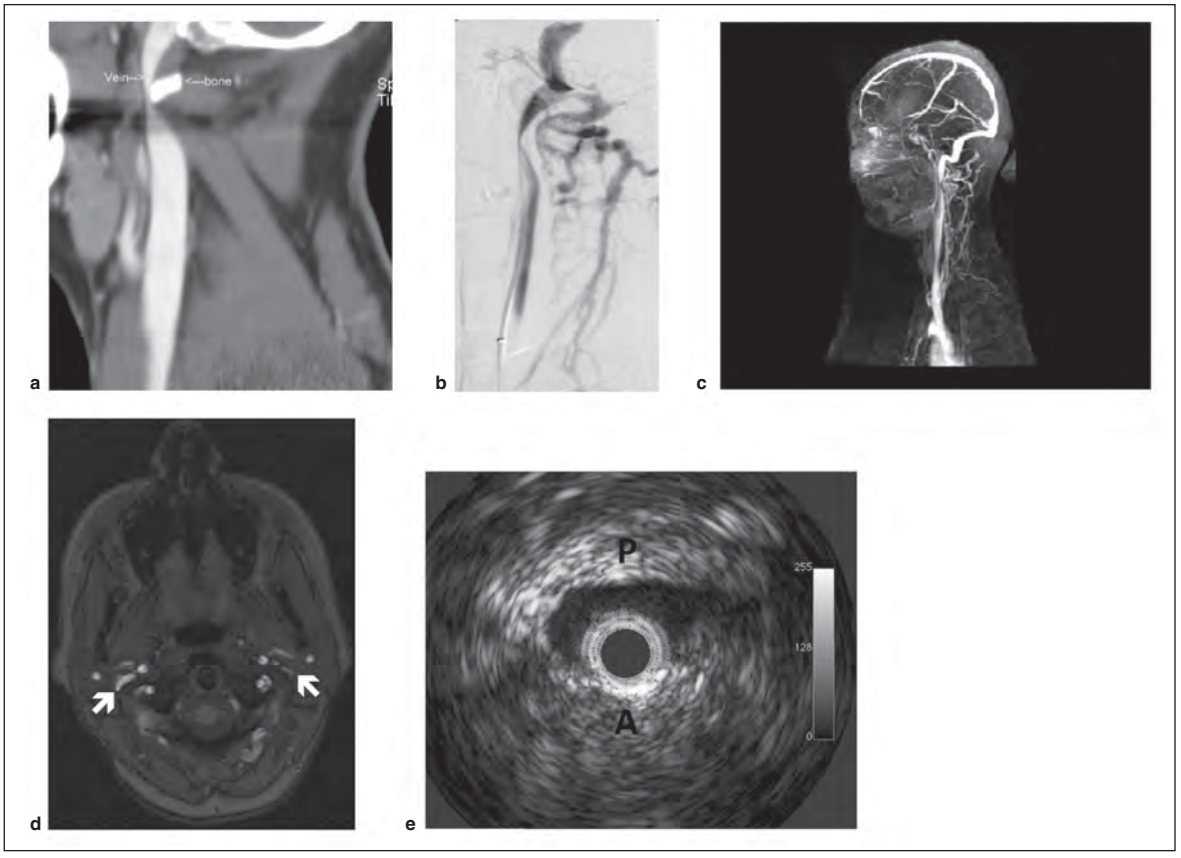


Figure 3 - Narrowing of the upper segment of the internal jugular vein.
(a) Sagittal image from CT venography of the neck with marked displacement and narrowing of the internal jugular vein by the bony lateral mass of the C1 vertebral body located posterior to the vein. (b) Lateral projection of conventional catheter-based contrast venography with extrinsic stenosis at the level of the C1 vertebral body. Multiple posterior collateral venous channels (vertebral, epidural, etc.) are evident. (c) MR venography of the head and neck presented in the sagittal view provides an example of a high internal jugular vein narrowing with associated collateral network of veins. (d) Axial MR venographic image with flattening of the upper segments of the internal jugular veins bilaterally, worse on the left side than the right (arrows). This is at the level of the C1 vertebral body where the transverse processes of C1 are directly posterior to the internal jugular veins. Posterior collateral channels, more prominent on the left side, are noted. (e) Intravascular ultrasound image of the internal jugular vein at the C1 level depicts asymmetric narrowing in the anterior-posterior dimension as the vein courses over the transverse process of the vertebral body.

The potential for consequences related to transient extrinsic internal jugular venous obstruction at this level have been highlighted in the neurosurgery literature (64). In an effort to investigate the cause of multiple reports of cerebellar hemorrhage secondary to venous infarction, not arterial bleeding, after supratentorial craniotomy or, less commonly, cervical spine surgery, Seoane and Rhoton performed microsurgical anatomical dissection of the internal jugular vein in the upper cervical segment in 36 adult cadaveric specimens. In every specimen examined, the posterior wall of the internal jugular vein rested against the transverse process of the atlas as the vein descended immediately below the jugular foramen. In 14 of the 36 specimens, the transverse process indented the posterior wall of the vein, causing the vein to be "slightly or moderately angulated" as it coursed over bone. In three specimens (8%), the vein was "severely kinked" and distorted (64). They concluded that obstruction of flow in the internal jugular vein at the site where the vein descends across the transverse process of C1 is the most likely cause of the venous hypertension that resulted in the cerebellar hemorrhage reported in numerous cases after supratentorial craniotomy. After examining the associated biomechanics of the region, they confirmed that rotating the head to the side opposite a supratentorial craniotomy and extending the neck, common practices in unilateral supratentorial craniotomy, further exaggerates the angulation and aggravates obstruction of the internal jugular vein at the C1 transverse process on the side ipsilateral to the craniotomy. The extent to which the obstruction of the internal jugular vein at C1 raises transmural intravenous pressure depends on the degree of communication between the transverse sinuses at the torcula and on the ability of the contralateral sinus to accommodate the increased flow caused by outflow obstruction of the opposite sinus.

This obstruction probably has no critical consequence in the presence of a torcula that communicates openly with transverse sinuses of equal size. However, if the transverse sinuses are different in size and do not communicate at the torcula, the venous pressure proximal to the obstruction may have a critical effect resulting in venous infarction (65-67). Browning reported in 100 cadaveric dissections that there was a common pool with free communication at the torcula in only 36% of cases, that the right and left transverse sinuses balanced in size with neither sinus being dominant in only 20% of cases, and that the right was dominant in 51% and the left was dominant in 29% (65). The more frequent dominance of the right transverse sinus correlated well with the fact that the majority of the literature cases of venous infarction and cerebellar hemorrhage followed right-sided supratentorial craniotomies.

In this regard, a previous imaging study of MS patients and healthy subjects observed a high incidence of venous stenosis at the level of the lateral mass of the C1 vertebral body in both groups (68). The presence of a mild indentation of the posterior wall of the internal jugular vein may be a physiologically irrelevant observation at this level, much like the similar narrowing of the left common iliac vein by an overlying right common iliac artery, frequently evident on CT imaging of the pelvis in patients presenting with complaints other than left leg symptoms. Indeed, there appears to be a spectrum of luminal compromise ranging in severity from mild external venous compression to severe narrowing by adjacent structures in a variety of anatomical locations. The exact nature, cause and potential consequence may be highly variable. Typically, it is only when these stenoses are critically severe that related symptoms may occur, such as left leg swelling, pain and occasionally venous thrombosis as noted in the May-Thurner syndrome.

It is interesting to note that in a 2005 published report of 188 consecutive patients undergoing either central venous access (40%) or interventional procedures (60%) such as transjugular liver biopsy via the internal jugular vein under ultrasound guidance, there were only two complications (69). One patient with renal failure required evacuation of a hematoma one week following placement of a tunneled dialysis catheter. The other complication occurred in the only patient in the study with a diagnosis of MS. He underwent tunneled insertion of a large caliber hemophresis catheter into the right internal jugular vein. Immediately after the procedure, the patient complained of left foot numbness never before experienced, as well as numbness of the upper chest.

In the mid-cervical segment, the internal jugular vein has a variable anatomical relationship with the carotid artery (69). Specifically, the position of the internal jugular vein relative to the distal common carotid artery and its bifurcation may influence the caliber of the more compliant vein causing a dynamic extrinsic compression of the venous lumen. A number of cross-sectional imaging and ultrasonographic studies have examined the anatomical relationship between the locations of the carotid artery and the internal jugular vein in the neck. Typically, at the mid-cervical level the internal jugular vein resides anterolateral to the carotid artery. This position of the vein between directly anterior and directly lateral to the carotid artery occurs in approximately 85% of the cases studied. In about 5% to 6% of cases, the internal jugular vein is positioned directly anterior to the carotid artery in the mid-neck (61). In either of these situations, where the internal jugular vein is located anterolateral or anterior to the carotid artery, conspicuous distortion of the contour of the vein by the adjacent artery is uncommon. In the 9% to 10% of cases in which the internal jugular vein is located directly lateral to the carotid artery, the luminal shape of the vein on cross-sectional imaging and its form on traditional catheter venography may be disfigured with an appearance typical of extrinsic compression – in this case, caused by the impinging, higher pressure, thick-walled artery. This is most commonly observed in cases with an ectatic, sweeping carotid bifurcation that smears across the neighboring internal jugular vein (Fig. 4). The venographic appearance of this effect is typical. The frontal venographic projection shows a medial parabolic impression on the lumen of the jugular vein and the lateral view has a telltale diagonal, slash-like effacement of the luminal column of contrast. The extent of luminal narrowing and prominence of collateral vessels associated with the extrinsic obstruction is variable and any related hemodynamic effects may be transient as clearly demonstrated by the changing venographic appearance that is observed with dynamic patient maneuvers, including neck rotation. It is possible that changing respiratory phases and the status of intravascular volume may also impact on the degree of any abnormality.

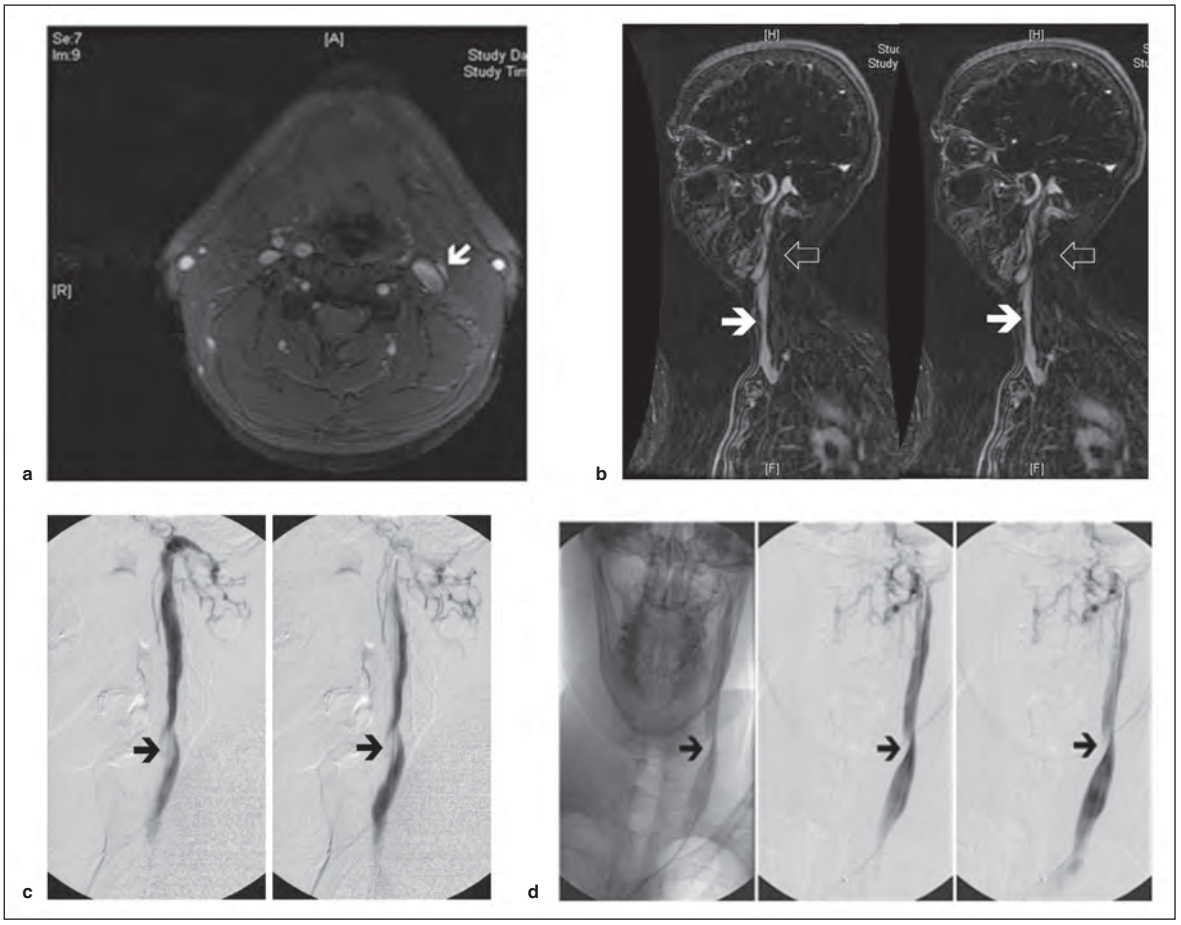


Figure 4 - Extrinsic narrowing of the mid-cervical segment of the internal jugular vein by the common carotid artery and its bifurcation. (a) Axial MR venographic image with crescentic, slit-like narrowing of the left internal jugular vein (arrow) by medial common carotid artery at its ectatic bifurcation. This appearance is observed only in cases where the vein is positioned directly lateral to the artery at this level. (b) The obstructive effect of this anatomical relationship is evident on the sagittal MR projection. The carotid artery at its bifurcation (open arrows) displaces and compresses the medial aspect of the internal jugular vein (arrows). (c) A similar appearance is noted on a lateral image from a conventional catheter-based venogram. Effacement of the venous contrast column with an obvious extrinsic narrowing (arrows) corresponding to the impression of the carotid artery on the internal jugular vein is apparent in the mid-cervical segment. (d) Frontal view of left internal jugular venogram with focal asymmetric medial narrowing of vein in its mid-cervical segment (arrows). The characteristic parabolic impression on the contrast column is caused by the carotid artery if it is immediately medial to the vein. If the carotid is tortuous at this level and directly medial to the vein, it may cause this type of appearance in the neutral or non-rotated head position. Rotation of the head to the side ipsilateral to the jugular under interrogation may accentuate the degree of obstruction and alternatively, rotation to the opposite side may relieve the narrowing. The dynamic nature of the "stenosis" is important to study.

In addition, below the carotid bifurcation at approximately the level of the C6 and C7 vertebral bodies and the thyroid gland, there may be transient dynamic compression of the internal jugular vein subjacent to the sternocleidomastoid muscle group. This may be apparent venographically as an extrinsic obstruction of the internal jugular, however, this narrowing may dramatically change with complete resolution following rotation of the head to the side contralateral to the vein in question (68).

By far and away, the segment of the jugular vein that has received the most scrutiny in CCSVI is the lower region that encompasses the jugular valve and immediately proximal regions in the inferior part of the vein (Fig. 5, over). Typically, there is one bicuspid valve in an internal jugular vein located just above its junction with the subclavian and brachiocephalic veins. There are reports in the literature of a wide spectrum of abnormalities associated with the valve, its annular wall attachment, and their effect on the diagnosis of CCSVI (6,24,70,71). Indeed, one of the Zamboni ultrasonographic criteria used to diagnose CCSVI involves imaging of a proximal (low or central) obstruction of the jugular in the region of the valve (24). Increased experience from multiple institutions has provided an opportunity to refine the description of these abnormalities into a few categories. Generally speaking, a distinction is now made between the observation of intraluminal abnormalities, such as webs, membranes, deformed valves, immoveable leaflets, malpositioned leaflets, etc., and circumferential, wall-

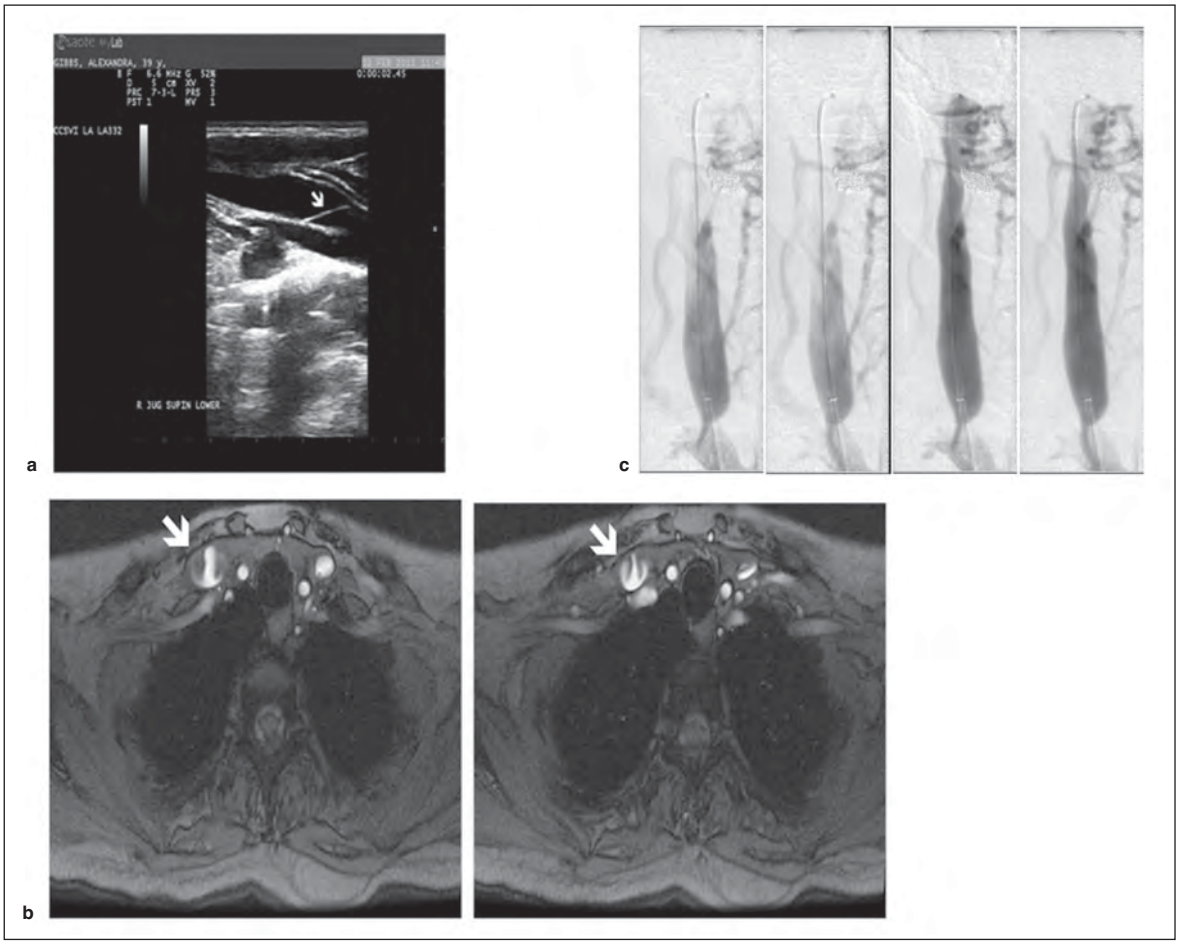


Figure 5 - Internal jugular vein narrowing within the valvular zone of the lower segment. (a) Longitudinal ultrasound image of the lower left internal jugular vein with septum (arrow) coursing across the transverse extent of the vessel adjacent to the valve. This abnormality is one of many that is increasingly recognized in the constellation of intraluminal lesions associated with the valvular region of the lower jugular. Many of these are associated with venous obstruction, flow abnormalities and a diagnosis of CCSVI. (b) Axial images from an MR venogram of the neck show prominent valve cusps (arrows) within the right internal jugular vein at the base of the neck. Conspicuous valvular architecture evident on MR imaging may be associated with a narrowed valvular orifice that is observed with other imaging modalities. (c) Right internal jugular venogram with fixed narrowing of the valve and obstruction to jugular venous drainage. Delayed emptying of the jugular vein following contrast injection and the presence of a robust collateral network are associated with the jugular venous insufficiency.

based constrictions that may be associated with the annulus of the valve (60-62,68,70-72).

The previously listed catalog of intraluminal lesions is by no means comprehensive and the nomenclature used to describe the abnormalities is not established. Presently, the terminology is descriptive, while the etiology (congenital or acquired) and relative significance of individual lesions remains unknown. It is consensually established that ultrasound imaging is currently the most sensitive non-invasive imaging modality to diagnose any intraluminal abnormalities and related flow disturbances. Catheter-based contrast venography and intravascular ultrasound have the ability to diagnose abnormalities in the valve region. Although venography is not capable of detecting the majority of intraluminal lesions associated with the valve, it does provide a global view of the vein, including the caliber of the valve orifice, and the ability to assess the tempo of contrast drainage through the jugular in a format that is familiar to interpret. Albeit invasive, catheter-based intravascular ultrasound imaging can confirm external ultrasound findings, complement the venographic assessment, and provide a valuable intraprocedural evaluation of intraluminal abnormalities pre- and post-intervention.

Recently, there have been reports of gross anatomical evaluation of tissues associated with the valve in the lower segment of the internal jugular vein. Diaconu et al., at the Cleveland Clinic, reported findings from the gross and microscopic evaluations of harvested bilateral internal jugular, subclavian, brachiocephalic, and azygos veins from 7 deceased MS patients and 6 non-MS controls (71). Veins were injected with silicone, dissected en bloc, incised longitudinally to expose the luminal surface, and fixed. All valves and structural abnormalities were characterized. They detailed marked valvular and other intraluminal abnormalities with potential he-

modynamic consequences in 5 of 7 MS patients (7 abnormalities) and in 1 of 6 controls (1 abnormality). These abnormalities included circumferential membranous structures (1 MS and 1 control), longitudinally-oriented membranous structures (3 MS), single-valve flap replacing the internal jugular vein valve (2 MS), and enlarged and malpositioned valve leaflets (1 MS).

If, indeed, there are more venous abnormalities affecting the jugular and azygos veins in MS patients than in non-MS subjects, how do any associated changes in the intra- and extracranial hemodynamics contribute to the development and progression of MS? The CCSVI conceptual framework argues that a vessel wall, whether arterial or venous, responds dynamically to changes in flow and pressure (5,46,73,74), such that the pulsatile shear stress and cyclic strain that the blood-brain barrier experiences with changes in venous blood flow can influence the degree of local inflammation and possibly the development of thrombosis and tissue injury (73). Laminar shear stress with normal venous flow promotes factors that maintain homeostasis and reduce inflammation, while disturbed, turbulent or reversed venous flow decreases shear stress and promotes a pro-inflammatory environment. Recently, Dolic et al. described the hemodynamic consequence related to extracranial intraluminal venous abnormalities; those subjects with a higher number of intraluminal abnormalities in the internal jugular veins presented with a higher number of collateral veins in the neck (68).

In an attempt to elucidate the role of iron, blood flow, lesion development and the general association of abnormal vasculature in MS, a number of researchers have been focusing on the application of advanced MR imaging methods (41,42). There is currently increasing use of MR imaging internationally that integrates the usual neurological MR protocol with a CCSVI imaging protocol. The former contains sequences that allow for anatomical and lesion information to be gathered, while the latter focuses on vascular anatomy, quantitative flow (for arteries, veins and cerebrospinal fluid) (75) and iron measurements. The combined protocol provides the tools necessary to probe the inter-relationship between flow and lesion development and other aspects of MS as a neurodegenerative disease.

The descriptive details of this protocol are provided in the appendix. Figures 3 through 6 demonstrate the anatomical information provided by MR angiographic/venographic (MRAV) methods. The conclusions drawn from anatomical imaging exclusively have not been convincing, with stenoses appearing in healthy subjects as well as MS patients. Nevertheless, the anatomical information has still proven useful in demonstrating congenital abnormalities, such as truncular venous malformations including a jugular trunk without any connection to the upper level jugular, a jugular trunk with a string-like connection to the upper level jugular, or membranous intraluminal material as mentioned above. In an imaging study of 200 MS patients, the first two findings were diagnosed in about 20% of the subjects (42).

In order to complement the anatomical information, it is important to examine the venous flow (42). It is not uncommon in MS patients to see many vessels in a contrast-enhanced scan, but to find flow in only one jugular vein. Figure 7 (over) presents the cross-sectional information used for flow quantification and figure 8 (over) provides four example flow profiles seen in normal con-

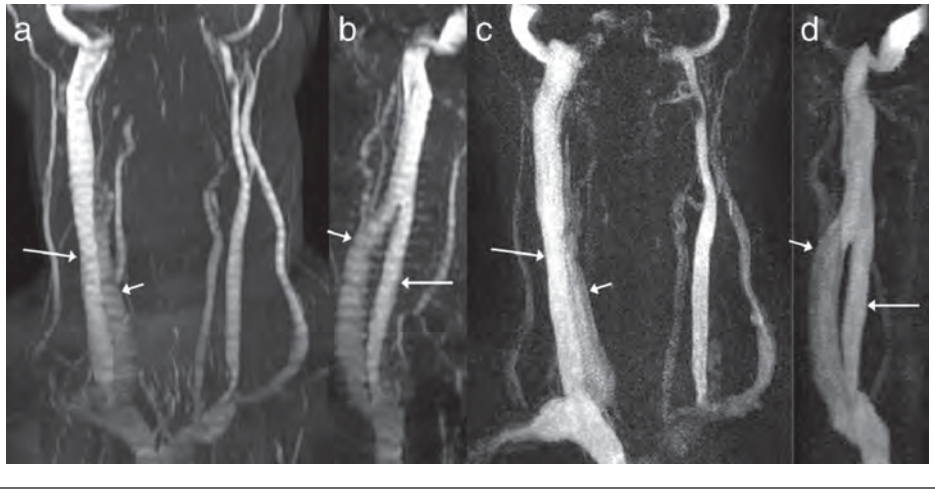


Figure 6 - Bifurcation of the right internal jugular vein into two components.
(a) Coronal 2D time-of-flight (TOF) MR venography (MRV) projection of the neck. The right internal jugular vein shows bifurcation into two components of approximately equal size near the mid-neck level; an anterior oriented component (short arrow) and a posterolateral oriented component (long arrow). The bifurcation of major veins may create obstructions of flow by generating turbulence in the venous drainage. (b) Sagittal 2D TOF MRV projection of the neck shows that the anterior component has a weak signal (short arrow) indicating possible obstruction or abnormal pattern of venous outflow compared with the posterolateral component (long arrow) which shows a strong, solid signal. (c) Coronal 3D contrast-enhanced (CE) MRV, with arterial signals removed to better view venous structures, shows consistency between modalities in the visualization of patency of the veins of the neck and bifurcation of the right internal jugular vein (arrows). (d) Sagittal 3D CE MRV of the neck shows the confluence of both the anterior component (short arrow) and the posterolateral component (long arrow) with the right subclavian vein. A change in signal intensity between the two fenestrated internal jugular vein components is evident.

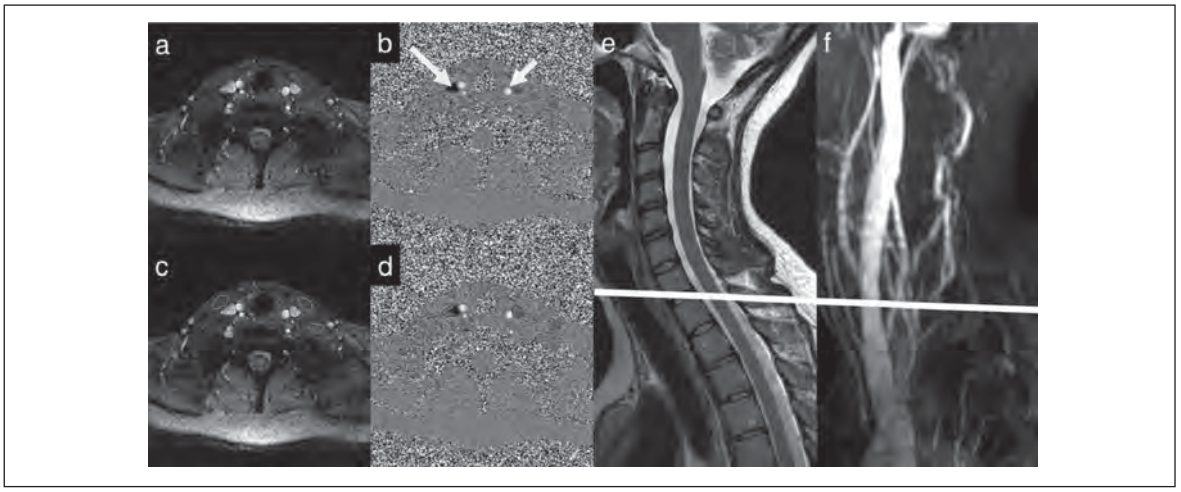


Figure 7 - Cross-sectional cut through C7/T1 showing arteries and veins. (a) Magnitude component of phase contrast slice showing the cross-sectional anatomy of the neck at the C7/T1 level with vessels highlighted due to blood flow through the slice. (b) Phase component of phase-contrast MRI (PC-MRI) slice showing the direction and speed of flow by signal intensity. The bright signal indicates flow in the caudal-cranial direction, the expected arterial flow as shown in the left common carotid artery (short arrow), and the dark signal indicates flow in the cranial to caudal direction, the expected venous flow as shown in the right internal jugular vein (long arrow). (c) Magnitude image with manually outlined contours of the vessels of the neck and regions of low flow, such as muscle, to correct for any phase offset. (d) Phase image with the manually outlined contours and their enclosed phase intensity which can be used to quantify blood flow variables. (e) Sagittal T2 weighted image shows the bright signal of the cerebrospinal fluid with clear visualization of the vertebral column. This image may be utilized to indicate any narrowing of the cervical CSF signals and place the appropriate positioning of the PC-MRI slice (white localization line) at the C7/T1 neck level. (f) Sagittal 2D time-of-flight MR venography projection shows the appropriate positioning of the PC-MRI slice (white localization line) perpendicular to the course of flow through the internal jugular veins.

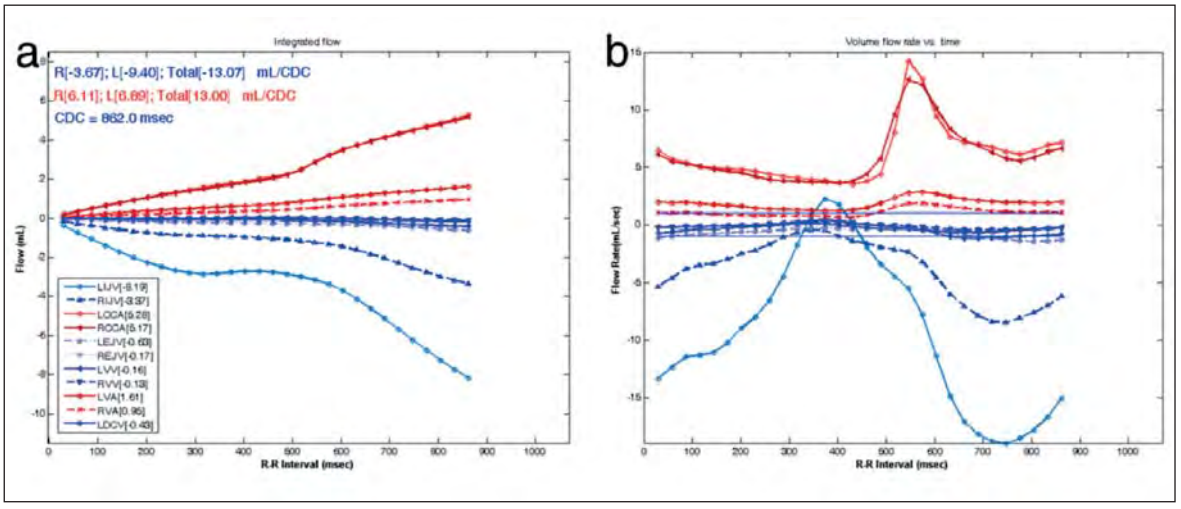
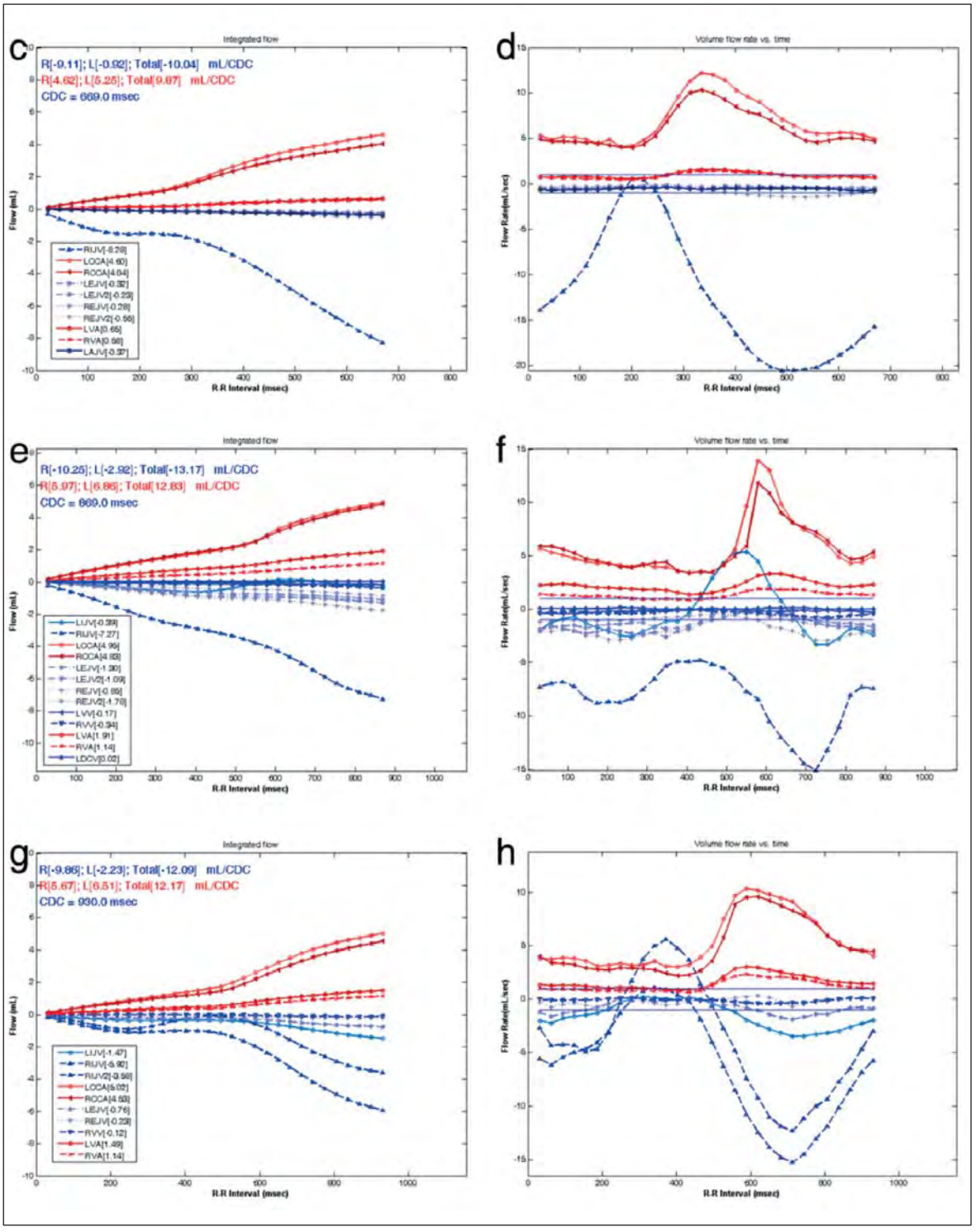


Figure 8 - A series of eight flow profiles from a normal control case and three MS cases.
The quantified integrated flow (a,c,e,g) and volume flow rate vs time (b,d,f,h) plots are shown for each patient taken at the lower neck level caudal to the confluence of the internal jugular veins with the subclavian vein. (a,b) In a normal control patient, the left internal jugular vein carries the dominant venous outflow and the right internal jugular vein carries the subdominant flow in a ratio of 2.43:1. The left internal jugular vein shows reflux prior to arterial systole as shown in (b) between 350 and 450 ms, however the flow in reflux is only a small fraction of the total venous outflow volume through the vessel and it occurs for a short period during the cardiac cycle. (c,d) In the quantified flow plots of a secondary progressive MS patient the right internal jugular vein carries over 83% of the total arterial flow and there is not a clear subdominant vein. An observed flow pattern in MS patients is the presence of venous outflow dominated by only one vein. Treatment of a patient's vessel which carries the majority of the venous outflow in the presence of no other clearly developed collateral may be inappropriate as it may unintentionally generate an obstruction of flow in the only functional drainage route. (e,f) The flow plots for a primary-progressive MS patient show the right internal jugular vein is the dominant vein with the right external jugular vein carrying the subdominant flow. The left internal jugular vein does carry some net venous outflow, however due to a strong reflux pattern which is delayed into the arterial systolic phase of the cardiac cycle, it carries only 3% of the



total arterial flow. This case is differentiated from the minor reflux shown previously in the normal control in that the reflux component negates potential venous outflow through the internal jugular vein. Abnormal venous outflow may be caused by anatomical narrowing such as stenosis, but also may be generated by unusual venous flow patterns as shown in this case. (g,h) Revisiting the relapsing-remitting MS patient shown in figure 6, this time with the quantified flow plots, shows another potentially abnormal flow pattern in which all vessels carry low flow or show reflux for a significant percentage of the cardiac cycle. In this case, the trend occurs between 275 and 450 ms in all veins and may indicate a transitory lack of appropriate venous drainage. The anterior component of the bifurcated right internal jugular vein (RIJV2) shows large reflux prior to arterial systole. Note that the pattern here is not delayed as shown in the previous example and occurs well before the arterial systolic phase.

trols and in MS patients. However, it is also possible that one may find that there are two normal functioning internal jugular veins with high flow in MS patients. There are a good number of MS patients who have only one functioning jugular (and often that is also the major source of drainage from the head) and it may be inappropriate to treat these dominant vessels. In the same study of 200 MS patients mentioned above (42), more than 25% had one dominant jugular (as defined by the criterion of a dominant to subdominant flow greater than 3:1). Finally, blood flow from the two dominant draining veins (usually, but not always, the two jugular veins) appears to have a lower threshold or cutoff of roughly 8ml/s, with lower total flow measured in about 25% of the MS patients evaluated – the majority of whom had venous stenosis (Fig. 9). On the other hand, none of the 18 normal control subjects had flow at or below this level measured in the dominant draining veins. It is possible that a low total internal jugular vein flow may prove to be a risk factor for developing MS.

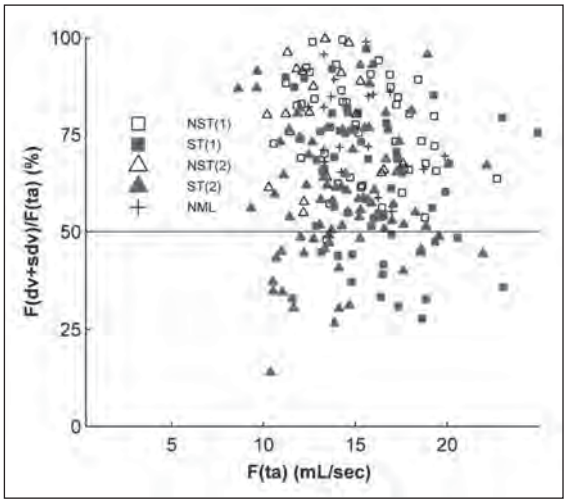


Figure 9 - Scatter plot of the sum of dominant and subdominant venous flow (F(dv+sdv)) vs the total arterial flow for 200 MS patients from two sites (100 from each site collected at approximately the C6 neck level). Note that F(dv+sdv) is shown in percentage of F(ta). Each population was divided into non-stenotic (NST) and stenotic (ST) groups based on cross-sectional area analysis of the internal jugular veins on axial 2D time-of-flight MRV. ST patients show at least one stenosis in either internal jugular vein and NST patients have no stenosis in either internal jugular vein. It is seen that for MS patients from both sites, almost all of the patients that have an F(dv+sdv)/F(ta) ratio of less than 50% are stenotic patients with only one NST patient meeting this criterion. Also, 18 normal controls were assessed with the same criterion. No normal control falls below a ratio of 50%.

Linking the autoimmune and vascular components of MS

Adhesion molecule and cytokine expression, along with factors that increase oxidative stress within the vein, can promote leukocyte migration from the bloodstream and attachment against the vein wall. This sequence of events is common within all vascular beds and is not exclusive to the blood-brain barrier (5,46,73). Once a leukocyte adheres to the vein wall, the cell rolls longitudinally along the wall until it sticks to a vulnerable location where it infiltrates the vein wall, insinuating between the endothelial junctions until it traverses the perivascular space. The inflammation and injury of the post-capillary venule at the so-called blood-brain barrier allows migration of other blood constituents, including erythrocytes which can lead to abnormal local accumulation of iron and lymphocytes. Iron in the CNS has an added inflammatory effect and both T and B cells within the tissue disrupt homeostasis and cause changes in osmotic pressure, pH, ion balance, etc., that can disable basic transport systems which are critical to normal cellular function (46). These reactions contribute to a neurodegenerative process that once established may result in sustained destruction with an eventual appearance of lesions typically described in late-stage MS plaques.

In this regard, is there any evidence to support this concept that MS may be primarily a degenerative disorder rather than an autoimmune disease? For years, John Prineas, a globally recognized authority in MS research, has been interested in exploring the nature of the earliest tissue evidence of MS in patients with active lesions (76). Recently, his research group published the results of a study of 26 newly-forming active MS lesions in the brains of 11 patients who died shortly after the acute onset of new symptoms (77). Their intent was to catalog the distribution of inflammatory cells within the lesions. Previously, the group reported that expanding MS lesions may exhibit prominent oligodendrocyte loss and apoptosis – hallmarks of characteristic MS pathological changes – in the absence of infiltrating lymphocytes. They detailed that parenchymal T and B cells were largely absent in areas of initial oligodendrocyte loss and in areas of degenerate and dead myelin infiltrated by myelin phagocytes. In contrast, in well-established trailing areas of complete demyelination packed with lipid macrophages, and, in some lesions, degenerating oligodendrocytes, showed large numbers of T and B cells, as well as immunoglobulin G (IgG)-positive plasma cells. Lesions in two exceptionally early cases contained a paucity of T and B cells, and no IgG-positive plasma cells. The authors' concluding interpretation stressed that "early loss of oligodendrocytes is a prominent feature in tissue bordering rapidly expanding MS lesions. Macrophage activity is largely an innate scavenging response to the presence of degenerate and dead myelin. The findings suggest that plaque formation has some basis other than destructive cell-mediated immunity directed against myelin or oligodendrocyte antigen" (77).

Concluding remarks

It is obvious that, more than 150 years after Charcot's initial description of MS, we still know far less than is necessary to offer patients and their families durable symptom relief, much less a cure for MS. All interested parties continue to be confronted with more questions than answers regarding the pathogenetic basis of MS, maintenance of the disease, subtypes of disease expression, and most effective and predictable therapeutic strategies. Historically, various aspects of vascular dysfunction

have been described in MS (78). Epidemiological studies suggest that patients with MS have a higher risk of ischemic stroke than individuals who do not have MS and multiple diagnostic modalities have demonstrated that patients with MS exhibit global cerebral hypoperfusion. CCSVI is a new hypothesis that has captured the front page interest of patients worldwide and although large, multi-institution trials (79) suggest it has an association with MS, the evidence to confidently support its fundamental role in the pathogenesis and progression of this disease is currently lacking.

It is readily appreciated that MS is a complex pathological process, not unlike certain cancers, with its etiology influenced by a variety of factors (genetic, infectious, environmental, dietary, inflammatory, etc.). The precise interplay and requisite role(s) of contributing factors that lead to the pathogenesis of MS is unknown. It is possible that the mosaic combination of individual etiological elements responsible for disease expression is different and even unique among those affected. It is currently unknown whether CCSVI represents one of the factors or risk factors that promotes or enables – along with others – the development of MS (35).

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APPENDIX

A General Magnetic Resonance Imaging (MRI) Protocol for the Study of Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis (MS) Patients

The CCSVI protocol uses a conventional neuro-MRI protocol for MS with additional specialized sequences to study the vasculature in the brain, neck and spine as well as the iron content in the brain. On the vascular side, both anatomical and flow information is collected. MRI is also operator-independent for the most part and the same protocols can be run on most manufacturers' systems. Potential biomarkers for CCSVI and MS can be identified from the data. MRI can also longitudinally track the progress of the disease over time via lesion counts and type, physiological changes like blood flow and cerebrospinal fluid (CSF) dynamics, and provide a baseline for future scans.

The following CCSVI imaging protocol is meant to complement conventional neurological examinations. The scans proposed for the CCSVI research protocol include: time-resolved contrast enhanced (CE) 3D MR angiography and venography (MRAV), 2D time-of-flight MR venography (TOF MRV), 3D volumetric interpolated breath-hold examination (VIBE), phase-contrast (PC) flow data at different levels in the neck and thoracic cavity, T2 weighted imaging (T2WI), T2 fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), and pre- and post-contrast T1 weighted imaging (T1WI) or magnetization prepared rapid gradient echo (MPRAGE) imaging. Perfusion scanning can also be added into this protocol for a small increment in time (roughly 3 minutes extra).

2D TOF MRV scans are used to detect blood flow in arteries and veins. Using a saturation band, any flow toward the head (arterial flow) will be saturated, and the flow toward the heart (venous flow) will be highlighted in a velocity-dependent manner. From this sequence, veins are well visualized and it can be determined if they are patent, occluded, or stenosed. Since the data are collected with high resolution, vessel cross-section can also be calculated to evaluate the degree of stenosis.

3D CE MRAV can also be used to evaluate vascular abnormalities. The scan uses a T1 reducing contrast agent which passes through all vessels and leads to increased signal for vessels in T1 weighted scans. From the data, 3D anatomical assessments can be done to evaluate vessel patency. Atresias, aplasias, truncular malformations, valve issues, and stenoses can be detected.

3D short TR, short TE VIBE pre- and post-contrast can be used to evaluate structural patency of vessels as well as inhomogeneous enhancement of the tissue. It is an alternative approach to the 3D dynamic CE approach just discussed and takes much longer (although it is still relatively fast).

PC images are used to assess flow dynamics in the head and neck veins and arteries, the azygos vein, and CSF at the C2/C3 cervical level. This information is critical because it can both corroborate and complement the information seen in the 2D TOF MRV and 3D CE MRAV. It is not uncommon to visualize the major veins only later to find that many of the veins have compromised blood flow. Often, there will be no clear anatomical evidence of venous stenosis, but the quantitative flow information will reveal abnormalities.

SWI is useful because the image contrast is based on the intrinsic susceptibilities of tissues. For example, veins are rich in deoxyhemoglobin which is paramagnetic and provides clear visibility of venous structures. Quantification of iron in the gray matter as well as lesions can be accomplished using T2*, phase or susceptibility mapping from the phase images. SWI is also useful in assessing blood products such as microbleeds and hemorrhages, possibly due to traumatic brain injury, vascular dementia, or MS. An interleaved SWI/MRA sequence can reveal arteries and veins on the order of a few hundred microns by means of a dual-echo sequence.

For more conventional imaging, T2WI is used to show tissue with long T2 components such as edema, CSF, tumors, and MS lesions. 3D T2 FLAIR is used because the images have suppressed CSF signal. FLAIR shows periventricular lesions well without the interference from CSF. Lesion quantity and volume can also be assessed with FLAIR. Eventually it may be possible to compare lesion volume with blood flow or patient's physiological changes over time. T1WI is used at two parts of the scanning protocol to image the head: initially before contrast agent injection, and after contrast agent injection. Lesions that enhance post-contrast are considered acute. Standardized guidelines for brain and spinal cord scanning in MS are widely available and differ according to whether used for clinical or research purposes (80,81).

PWI is used to evaluate the hemodynamics of the brain. From this data it is possible to assess mean transit time (MTT) which is the time it takes for contrast agent to pass through the microvasculature, the cerebral blood volume (CBV) and the cerebral blood flow (CBF).

In summary, the use of quantitative MR imaging methods such as those described above may provide objective evidence for flow abnormalities in MS patients.