



Raised venous pressure as a factor in multiple sclerosis

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Received 22 September 2007; accepted 6 October 2007

Summary It is hypothesised that the inflammatory condition seen in MS and the progressive myelopathy that is being successfully halted by obliteration of dural arteriovenous fistulas (DAVFs), may actually be two sides of the same coin. Excessive venous hypertension can stretch vein walls sufficiently to separate the tight junctions between endothelial cells forming the blood-brain-barrier (BBB). Colloids, etc., but not necessarily erythrocytes, could then pass through the exposed porous basement membranes. The resulting changes in osmotic pressure, etc. would disrupt the axon and dendrite internal transport systems, leading to their disintegration. The normal inflammatory processes which would follow, might be indistinguishable from those associated with autoimmune disease.

Ascending progressive myelopathy and disablement are associated with an intracranial DAVF when its outflow enters the spinal venous system and descends past the cervical region. This can be arrested, and some degree of recovery produced, if the DAVF can be successfully eliminated or blocked. However, if the DAVF outflow is entirely into the spine, intracranial venous pressure may be normal and so there is nothing to alert the clinician to the presence of an intracranial DAVF.

It is suggested that where spinal MS has been diagnosed from clinical observations, patients should be referred for angiological investigation to search for DAVFs within the head to identify any treatable subjects.

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Introduction

MS relation to veins

Multiple sclerosis (MS) is characterized by multiple plaques of demyelination within the brain and/or spinal cord, currently attributed to an autoimmune process, following some as yet unidentified event. Close relatives have increased chance of developing

MS, but no known links exist between MS and any infection [1]. Early investigators noted that plaques formation was not completely random. In the spine there appeared to be an underlying segmental pattern. Plaques in the CNS generally appear to be related to veins. Tan et al. [2] studied 95 brain MS lesions using magnetic resonance imaging (MRI) techniques in vivo. They found a central vein was visible in all but one. The lesions typically had a basically ovoid shape whose long axis correlated well with the course of the vein, whereas using the same technique on cases of hypoxic ischemic

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white matter, lesions bore no relationship to venous patterns. Kidd et al. [3] found large cortical lesions, which pass around gyri, were likely to reflect involvement of the central vein of the gyrus.

Sources of spinal venous hypertension

Retinopathy and optic nerve pathology are frequent early clinical signs of MS but also occur with acute raised intrathoracic pressure as blood is forced back into the head producing surges of intracranial venous pressure ('Valsalva retinopathy') [4–13]. Apart from such acute events, chronic venous hypertension may result from arteriovenous anastomoses (AVA), in particular dural arteriovenous fistulas (DAVFs), within the head [14,15] or spine [16]. Borden et al. [17] recognised the various pathological significances of the drainage paths of intracranial dural arteriovenous fistulas (DAVFs). They suggested three categories; type I draining entirely within the skull, type III draining entirely into the spinal venous system, and type II with mixed drainage. Using in vivo magnetic resonance imaging (MRI), Kwon et al. [18] observed that distension of ophthalmic veins occurs in grade II but not in grade III. In contrast spinal dilated leptomeningeal or medullary vessels were not seen in grade I, but were in 100% of grade III cases. Cognard et al. [15] found that in cases where drainage was purely spinal, progressive myelopathy occurred in 50% of cases. Brunereau et al. [14] compared two such spinal drainage groups and found that where grade III drainage could be traced to the lumbar region it was clinically associated with slowly progressing ascending myelopathy involving first the lower and then the upper limbs. On the other hand, where drainage could only be traced as far as the cervical region of the cord, myelopathy did not seem to occur. Fistulas associated with myelopathy also occur in the spinal vasculature, where they may be recognised by the occurrence of reversed or severely reduced local spinal vein flows. The strong clinical links between disability and factors producing CNS venous hypertension, raises the possibility that the unknown initial event [1] might be mechanical.

Hypothesis

That the initial event in one form of MS is endothelial cell tight junction separation due to radial distension of veins in the head and/or spine by excessively raised transmural pressures. Overt failure of the vein wall may not occur, but separation of endothelial tight junctions would result in local

breaching of the blood-brain-barrier (BBB). The resulting changes in osmotic pressure, pH, Na/K balance etc. would then disable the intra-axon and intra-dendritic transport systems, on which these cell extensions depend for normal function, leading to their degeneration. This in turn would trigger an intensive but completely normal inflammatory scavenging reaction, secondary to the primary damage caused by disruption of the BBB. Hence, anti-inflammatory treatments would have no effect on the incidence of this form of MS. Arteriovenous anastomoses of various kinds, or venous obstruction would provide the underlying chronic venous hypertension.

The primary mechanism, venous wall disruption

West et al. [19,20], studying endothelium in lung alveolar capillaries with electron microscopic techniques, observed that as pressure was raised, endothelial failure occurred in three stages. The first involved rupture of the tight junctions between adjacent endothelial cells, Fig. 1(1). Basement membranes remained intact, but as these are inherently porous the vessel walls became permeable. The next stage was the formation of pressure sensitive pores, Fig. 1(2). These were minor tears in the basement membranes, which when stretched

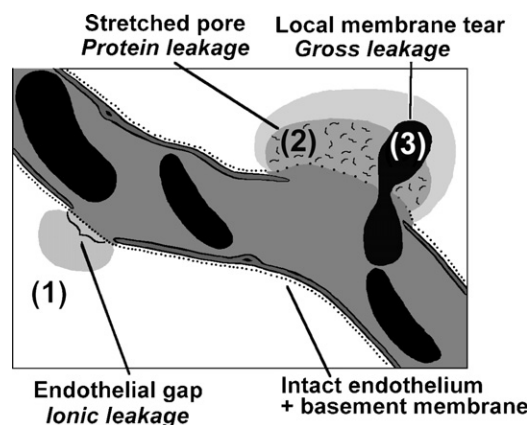


Figure 1 Endothelial cell junction rupture under raised lumen to perivascular pressure. Stage 1. Simple endothelial cell junction separation allows plasma electrolytes and small proteins to pass through the exposed basement membrane (a fibrous mat) which remains intact. Stage 2. At higher pressure small tears appear in the basement membrane allowing larger proteins to pass through. Stage 3. The tears get stretched wider, so that the higher the dilating pressure the larger the proteins passing until ultimately erythrocytes deform and squeeze through.

further open at higher pressures, allowed larger molecules to pass but reverted to blocking them again when the pressure was lowered. Up to this stage, affected veins might appear normal by light microscopy, since no hemorrhage had occurred. Finally, the walls ruptured sufficiently for erythrocytes to be expelled through them, Fig. 1(3). In the present context, only the initial leakage stages (inter-endothelial gap porosity and stretched pore) are required to disrupt the BBB and hence axonal function. Regions of multiple microleakages will be defined by pressure distribution and local wall strengths. These microleakages will act as "seeds" from which plasma components will spread, eventually coalescing to form visible areas of plaque formation.

Axon and dendrite metabolic factors

While intracellular diffusion provides adequate transport within cell bodies, simple diffusion is inadequate along axons and dendrites. Axons are known to have three transport systems [21], a slow outward one at 1–4 mm/day carrying materials necessary for axon growth and axoplasm maintenance, a fast transport at 50–400 mm/day conveying membranous organelles, and a slightly slower, retrograde, transport returning "used" membranous components back to the cell body for recycling. If, as a result of axon injury, abnormal constituents arrive in this return flow, they appear to signal the cell body to facilitate axon repair or regrowth [21]. Failure of these transport systems would starve axons and dendrites of nutrients, ATP, etc. [22], and the cell body would not be stimulated to reparative action. Cell bodies have an ability to maintain osmotic balance [23] by increase or decrease of the manufacture of intracellular 'osmolytes', which can accumulate to high concentrations without altering internal cell function [24]. So while neuron, oligodendrocyte, and astrocyte bodies may be able to tolerate osmotic insults by generating compensatory internal osmotic pressures, their extensions will become desiccated. This in turn may break communication between axons and their accompanying oligodendrocytes and astrocytes. It has been observed that where oligodendrocytes do re-extend in a potential recovery phase they do not necessarily 'recognise' axons although passing in close proximity [25]. The result will be the degeneration of myelin sheaths in a general Wallerian degeneration peripheral to each vein leakage site. Cord atrophy has been found to be principally in white matter and Miller et al. [26] found a remarkable preponderance of

loss of smaller diameter axons. Smaller diameter axons will have a larger surface area to volume ratio and so would dehydrate faster than larger ones, especially if they are naturally non-myelinated. Johnson and Becker [27] show a series of MRI images, which indicate that the initial spreading events occur over a period of about 5 weeks, and activity ceases after about 4 months.

Application to observed patterns of damage

Cord venous system

The cord is surrounded by two venous plexuses. The space between the dura and the periosteum is filled with a fatty substance through which a venous plexus of interconnected valveless tubes completely wraps the spinal dural sac like a lacework sleeve. This is known as the internal vertebral, or epidural plexus. It allows flow up, down, and around the cord, Fig. 2a. This sleeve functionally extends vertically from the lumbar region to intracranial sinuses. If a DAVF outflow was directed into this epidural venous plexus it would become a pressure barrier to spinal cord return flow via the radicular veins. A similar outer plexus surrounds the vertebral bodies and their spinal wings, Fig. 2b. The two venous plexuses communicate by intervertebral veins through the intervertebral foramina, in company with the mixed nerves Fig. 2a. Segment veins drain ultimately mainly into the azygos vein system. The veins of the spinal cord itself are situated in the pia mater in which they form a tortuous venous complex. They drain segmentally, via radicular veins Fig. 2a, into the internal venous plexus. If outflow in one segment were to become opposed, pressure would build up in a retrograde manner until sufficient to drive blood to the collateral paths in the neighboring segments. If the pressure were sufficient to cause endothelial-separation a patch of demyelination would appear near the affected intervertebral foramina. Since this inner sleeve wraps round the cord, the pressure rise would also be partially communicated to spinal veins on the other side. Van de Kuip et al. [28] found that radicular veins contain smooth muscle in their walls of unknown function. Their constriction would impede cord outflow and might trigger episodes of damage.

Brain venous system

In the brain it has been recognised that plaque formation has a predilection for cortical and

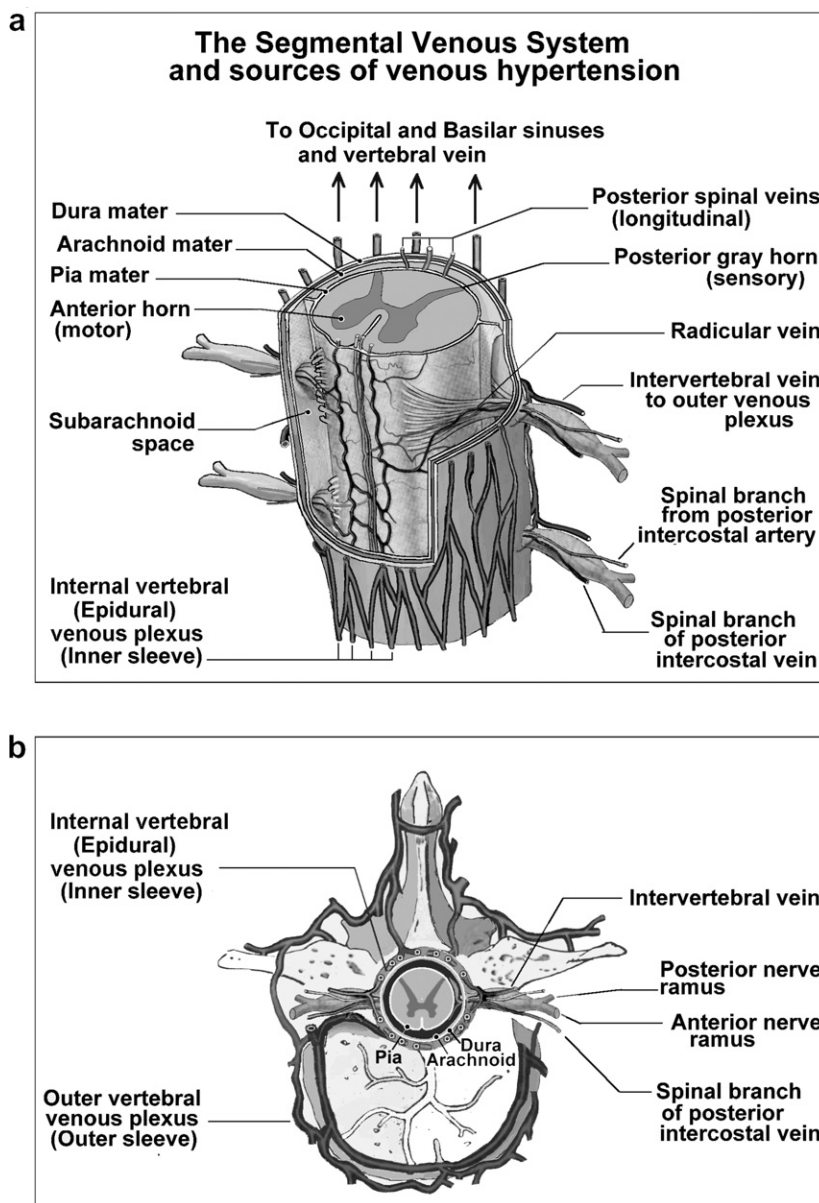


Figure 2 The complex spinal venous drainage system. The veins of the spinal cord itself are situated in the pia mater and have longitudinal and lateral components. Near the base of the skull they unite to form two or three small trunks which communicate with the vertebral veins, and end in the inferior cerebella veins or in the inferior petrosal sinuses. Segmentally they drain through the Radicular Veins into the Inner Vertebral (Epidural) Plexus, which is a “lacework” sleeve lying on the spinal dura mater. (a) An outer venous sleeve surrounds the vertebra (b) and is referred to as the Outer Vertebral Venous Plexus. The two plexuses communicate through intervertebral veins.

periventricular positions. This is understandable on the basis of perivascular pressure. Deep within the brain substance neighboring veins provide mutual support as they press against each other through the intervening tissue. Those neighboring CSF spaces (subarachnoid space, brain ventricles) will receive no such support since CSF can be displaced into the spinal spaces, relieving CSF pressure (Monro–Kellie doctrine [29]). Brain surface veins and venules are therefore most at risk of over distension initiating plaque formation.

Discussion

Dutta and Trapp set out hallmarks of classic MS [22] as “breakdown of the BBB, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axon degeneration”. They considered that axon loss occurs at the onset of MS. Neurofilament-positive swellings detected along dendrites and axons suggested disruptions of normal cellular transport. The efficacy of anti-inflammatory therapeutics was of minimal or no benefit in terms of

progression of neurologic disability in patients with relapsing–remitting, secondary progressive, or primary-progressive forms of MS.

Comparing these features with this venous pressure/endothelial-separation hypothesis, loss of the blood-brain-barrier is the fundamental mechanism. Disruption of normal transport along axons and dendrites would be a natural consequence, secondary to the primary BBB damage. An inflammatory response would be expected, but be normal not autoimmune.

Demyelination, axon and oligodendrocyte degeneration would be expected to follow. Anti-inflammatory measures would only alter the incidence (aggression) of the condition if some unrelated infection etc. were already weakening the vein walls.

Where myelopathy arises from this hypothetical mechanism it may be possible to arrest its progress. Foremost causes of chronic CNS venous hypertension appear to be related to forms of arteriovenous anastomoses or fistulae especially DAVFs, as evidenced by the beneficial outcome of their removal when recognised. Several techniques have proved beneficial; surgical [30], embolisation [31–34], and stereotactic radiosurgery [35,36]. However, where intracranial DAVF drainage is virtually entirely into the spinal venous system, intracranial venous pressure may be normal and brain function be normal. There will be no clinical indication of the presence of an intracranial arteriovenous connection.

Conclusions

Where clinical signs appear within the head (progressive visual disturbance, etc.) venous hypertension resulting from fistulas is being recognised and treated. Once the fistula has been located a variety of therapies are available to block it and restore normal pressure in the draining veins which arrests further progression. However, as Chen et al. [37] point out, “Diagnosis of an intracranial dural arteriovenous fistula (DAVF) with perimedullary venous drainage is challenging because the presenting symptoms are usually related to dysfunctions of the spine, not the brain. Repeated spinal angiograms are usually performed before the diagnosis is finally made by cerebral angiography.” While restoration of normal venous pressure cannot restore destroyed axons, etc., it has been observed clinically to arrest further loss of function and consequently will not come to pathological examination. If axon loss caused by venous hypertension in the CNS mimics many of the characteristics of

autoimmune MS, the presence of an intracranial DAVF draining principally extra cranially may not be considered. It is suggested that angiologic examination of patients apparently suffering from autoimmune MS might detect those with some form of unsuspected AVA, which could be treated with appropriate therapy.

Acknowledgements

This study was initiated at the suggestion of Dr. F. Schelling who deserves the credit for recognizing, from the pattern of injuries in MS, the possibility of a venous pressure origin. Much of this study was founded on observations laid out in his on-line book <http://www.multiple-sclerosis-abc.org> which surveys and analyses the many hypotheses that have been advanced for this condition. The author is grateful to Dr. Schelling for introducing him to this fascinating field of research, and hopes Dr. Schelling’s contribution to it will be properly recognised.

References

- [1] Kumar P, Clark M. Neurological diseases. In: Kumar P, Clark M, editors. *Clinical medicine*. Edinburgh: Elsevier Sanders; 2005. p. 1173–271.
- [2] Tan IL, van Schijndel RA, Pouwels PJW, et al. MR venography of multiple sclerosis. *Am J Neuroradiol* 2000;21:1039–42.
- [3] Kidd D, Barkhof F, McConnell R, Algra PR, Allen IV, Revesz T. Cortical lesions in multiple sclerosis. *Brain* 1999;122:17–26.
- [4] Jones WL. Valsalva maneuver induced vitreous hemorrhage. *J Am Optom Assoc* 1995;66:301–4.
- [5] Avins LR, Krummenacher TK. Valsalva maculopathy due to retinal arterial macroaneurysm. *Ann Ophthalmol* 1983;15:421–3.
- [6] Kocak N, Kaynak S, Kaynak T, Oner HF, Cingil G. Unilateral purtscher-like retinopathy after weight-lifting. *Eur J Ophthalmol* 2003;13:395–7.
- [7] Linnemann CC. Bordetella. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. *Oxford textbook of medicine*. Oxford: Oxford University Press; 1996. p. 587.
- [8] McKendrick GDW. Bordetella infections; whooping cough. In: Scott RB, editor. *Price’s textbook of the practice of medicine*. Oxford: Oxford University Press; 1978. p. 49–51.
- [9] Geddes JF, Talbert DG. Paroxysmal coughing, subdural and retinal bleeding: a computer modeling approach. *Neuro-path Appl Neuro* 2006.
- [10] Ladjimi A, Zaouali S, Messaoud R, et al. Valsalva retinopathy induced by labour. *Eur J Ophthalmol* 2002;12:336–8.
- [11] Sbeity ZH, Mansour AM. Recurrent retinal vein occlusion after playing a wind instrument. *Graef Arch Clin Exp Ophthalmol* 2004;242:428–31.
- [12] Georgiou T, Pearce IA, Taylor RH. Valsalva retinopathy associated with blowing balloons. *Eye* 1999;13:686–7.

- [13] Roberts DK, MacKay KA. Microhemorrhagic maculopathy associated with aerobic exercise. *J Am Optom Assoc* 1987;58:415–8.
- [14] Brunereau L, Gobin P, Meder JF, Cognard C, Tubiana JM, Merland JJ. Intracranial dural arteriovenous fistulas with spinal venous drainage: relation between clinical presentation and angiographic findings. *Am J Neuroradiol* 1996;17:1549–54.
- [15] Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. *Radiology* 1995;194:671–80.
- [16] Asai J, Hayashi T, Fujimoto T, Suzuki R. Exclusively epidural arteriovenous fistula in the cervical spine with spinal cord symptoms: case report. *Neurosurgery* 2001;48:1372–6.
- [17] Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. *J Neurosurg* 1995;82:705–6.
- [18] Kwon BJ, Han MH, Kang HS, Chang KH. MR imaging findings of intracranial dural arteriovenous fistulas: relations with venous drainage patterns. *Am J Neuroradiol* 2005;26:2500–7.
- [19] West JB, Tsukimoto K, Matheu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. *J Appl Physiol* 1991;70:1731–42.
- [20] West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries: role in lung and heart disease. *Lancet* 1992;340:762–7.
- [21] Cormack DH. Nervous tissue and the nervous system. In: Cormack DH, editor. *Ham's histology*. Philadelphia: Lippincott; 1987. p. 338–87.
- [22] Dutta R, Trapp BD. Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology* 2007;68(Suppl. 3):S22–31.
- [23] Parker JC. In defense of cell volume? *Am J Physiol* 1993;265:C1191–200.
- [24] Lee JH, Arcinue E, Ross BD. Brief report: organic osmolytes in the brain of an infant with hypernatremia. *New Engl J Med* 1994;331:439–42.
- [25] Chang A, Tourtellotte WW, Rudick R, Trapp BD. Premyelinating oligodendrites in chronic lesions of multiple sclerosis. *New Engl J Med* 2002;346:165–73.
- [26] Miller DH, Barkhof F, Frank JA, Parker GJM, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain* 2002;125:1676–95.
- [27] Johnson KA, Becker AB. Inflammatory or infectious disease: multiple sclerosis. In: Johnson KA, Becker AB, editors. *The whole brain atlas*. Harvard: Harvard Medical School; 2003. Available from: <http://www.med.harvard.edu/AANLIB/>.
- [28] Van der Kuip M, Hoogland PVJM, Groen RJM. Human radicular veins: regulation of venous reflux in the absence of valves. *Anat rec* 1999;254:173–80.
- [29] Mokri B. The Monro–Kellie hypothesis: application in CSF volume depletion. *Neurology* 2001;56:1746–8.
- [30] Sundt TMJ, Piepgras DG. The surgical approach to arteriovenous malformations of the lateral and sigmoid dural sinuses. *J Neurosurg* 1983;59:32–9.
- [31] Halbach V, Higashida RT, Hieshima GB, Reicher M, Norman D, Newton TH. Dural fistulas involving the cavernous sinus: results of treatment in 30 patients. *Radiology* 1987;163:437–42.
- [32] Dawson III RC, Joseph GJ, Owens DS, Barrow DL. Transvenous embolization as the primary therapy for arteriovenous fistulas of the lateral and sigmoid sinuses. *Am J Neuroradiol* 1998;19:571–6.
- [33] Steiger HJ, Hanggi D, Schmid-Elsaesser R. Cranial and spinal dural arteriovenous malformations and fistulas: an update. *Acta Neurochir* 2005;94(Suppl.):115–22.
- [34] Asakawa H, Yanaka K, Fujita K, Marushima A, Anno I, Nose T. Intracranial dural arteriovenous fistula showing diffuse MR enhancement of the spinal cord. *Surg Neurol* 2002;58:251–7.
- [35] Pollock BE, Nichols DA, Garrity JA, Gorman DE, Stafford SL. Stereotactic radiosurgery and particulate embolization for cavernous sinus dural arteriovenous fistulae. *Neurosurgery* 1999;45:459.
- [36] O'Leary S, Hodgson TJ, Coley SC, Kemeny AA, Radatz MW. Intracranial dural arteriovenous malformations: results of stereotactic radiosurgery in 17 patients. *Clin Oncol (R Coll Radiol)* 2002;14:97–102.
- [37] Chen CJ, Chen CM, Lin TK. Enhanced cervical MRI in identifying intracranial dural arteriovenous fistulae with spinal perimedullary venous drainage. *Neuroradiology* 1998;40:393–7.