Is Multiple Sclerosis Caused by the Jaw and Cranial Bones?

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Introduction

Multiple sclerosis (MS) has traditionally been considered an inflammatory autoimmune disease of the central nervous system (CNS). The autoimmune hypothesis has prevailed for over 70 years and has largely dictated the research direction and treatment modalities offered to MS patients. A recent study revealed that the interferon beta drugs widely prescribed in MS have no effect on the long-term outcome in relapse-remitting (RR) MS patients ([Ref], [Ref]). No drugs have ever been shown to be effective for the chronic progressive forms of MS, secondary progressive (SP), primary progressive (PP), and progressive-relapsing (PR) ([Ref]). A recent review from the Mayo Clinic on the status of MS as an autoimmune disease is a somber reminder of the sorry state of MS research ([Ref]).

The vascular relationship to MS has a long history, stretching all the way back to Cruveilhier in 1839 who described vascular abnormalities in MS. In 1863, Rindfleisch observed an engorged blood vessel in the center of a plaque. In 1863 Charcot described vascular obstruction in MS. In the 1930s, Putnam attempted to cause MS in animals by vascular obstruction. In 1963, Fog noted that MS lesions appear around small veins and that plaques definitely followed the course of veins. In the 1980s, Schelling described the role of venous reflux in the genesis of the cerebral and spinal lesions ([Ref]). In 2006, Zamboni published a study noting the similar iron deposition patterns between chronic venous disease and MS. In 2009, Zamboni et al. proposed chronic cerebrospinal venous insufficiency (CCSVI) as a factor in MS. Four hemodynamic patterns of CCSVI were identified which were said to correlate to MS phenotype.

In 2010, Williams et al. published a breakthrough real-time study demonstrating marked lateral displacement of the temporal bones in MS patients during bruxism ([Ref]). Using a pulse phase locked loop (PPLL) device, MS patients were found to have a bilateral temporal bone displacement six times greater than healthy controls during a sustained clenching force of 100 pounds of pressure. It was hypothesized that reduced bone density in MS patients can increase the displacement along the cranial sutures, possibly allowing skull bone deflection to create damaging pressure waves.

By methodically tying together the work of Schelling ([Ref]), Williams, and countless others, a cogent understanding of MS is possible. **MS proper is not an autoimmune condition at all but a chronic biomechanical disease of the CNS.** Due to the biomechanical and hydrological forces acting on the CNS in this model of MS, an overhaul of CSF and ISF physiology will be necessary for a proper elucidation of the pathology. The existing MS phenotypes are inadequate relics from the autoimmune era and MS will surely require a complete redefinition. However, since much of the available literature is based on these clinical entities, they will necessarily be used here.

The Autoimmune Fail

An exhaustive criticism of the autoimmune hypothesis is unnecessary here and has been done elsewhere. MS has never been proven to be an autoimmune disease despite textbooks and research articles adopting language as if it were ([Ref]). Ebers et al. found no association between MS and other autoimmune diseases among MS patients and their first-degree relatives ([Ref]). At least two studies have
found that the PTPN22 allele is associated with a number of autoimmune conditions but not MS, indicating a different pathogenesis (Ref, Ref).

Schelling has criticized the autoimmune theory for decades and points out the elephant in the room: the primary mechanism of injury in the autoimmune hypothesis is, after 70 years of research, ludicrously vague, speculative, and unable to explain any of the observed patterns of MS or any of its specific or peculiar characteristics. Wootla et al.’s summary of the mechanisms of injury perfectly illustrates this reality [emphasis added],

In MS, for an oligodendrocyte to be injured by inflammatory cells, it must express MHC class I or class II genes. CD8+ T cells can then engage a novel protein that is expressed in the context of class I MHC. CD8+ T cells would then secrete perforin, granzyme, or other factors that may directly injure or kill the oligodendrocyte resulting in demyelination. Antibodies, through molecular mimicry, may recognize autoantigens of the CNS and can also injure the oligodendrocyte by binding to the surface of the cell and, in association with complement, may induce direct injury to myelin or the oligodendrocytes. This partially leads us to the autoimmune hypothesis. In addition, the B cells may also present virus antigens in the context of class II MHC molecules. The oligodendrocyte or microglia itself may also express class II MHC. This presentation of the viral antigen must be processed, which allows the CD4+ T cells to be engaged with class II MHC to induce injury, the common mechanism of injury presumed to be present in experimental autoimmune encephalomyelitis. The oligodendrocyte may die as a consequence of direct and persistent virus infection. These mechanisms of injury may be independent or occur concurrently in each brain. All of these mechanisms lead to demyelination that the host may correct by transient remyelination. Ultimately, the demyelination process overtakes remyelination resulting in axonal damage, thus leading to permanent neurologic deficits.

At the present time, there is no clear evidence that these patterns of injury relate to various stages of the disease course and do not correlate with the clinical subtypes of relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, or primary progressive multiple sclerosis, although this is yet to be determined.

Indeed, the final product after many years of research is an absurdly speculative cascade of events with even a mysterious, unidentified viral antigen thrown in for good measure. Even if such a process were responsible, it is not readily apparent how it can explain any of the clinical presentations of MS in actual patients. A great deal of vagueness has been allowed to pass in MS research thanks in large part to a conveniently vague MS disease specification as Schelling explains [emphasis added],

As it is presently understood, the term "multiple sclerosis" conceals, in a threefold manner, the nature of any disease process to which it is applied:

1. There is the misleading clinical multiple sclerosis conception, which reflects the setting apart of certain cryptic disease processes simply by means of two quantitative properties: number and time. No facts have ever been presented to prove that this manner of determining the presence or absence of multiple sclerosis by the timing of unexplained neurological episodes is actually
2. No less confusion has been created in additionally specifying multiple sclerosis by two different, each sufficiently broad histological terms which are supposed to provide a morphological lesion specification coextensive with the neurological dysfunctional one. Here the early all-inclusive label "grey degeneration" became the forerunner of the expression "(multiple) sclerosis", implying that the disease was due primarily to a scarring process. Since some researchers felt that the latter lesion definition (yet not the term itself) was too narrow, the vague notion "primary inflammatory demyelination" came to be used. Nowadays, in certain circles, multiple sclerosis is considered to be caused by some sort of unexplained inflammatory cellular infiltrate of auto-aggressive immunocytes causing a specific myelin destruction (less obtrusive damages to other tissue components being, without qualms, passed over in silence). But the distinctiveness of this disease entity has never been substantiated by any specific exemplary observations.

3. Even the most fundamental differences in the lesion patterns shown by individual instances of (clinical) multiple sclerosis were eventually simply glossed over in conceiving of multiple sclerosis as the result of some random form of lesion spread, effected by some essentially cryptogenic "disseminated encephalomyelitis". The epithet "disseminated" thereby complicates matters by

- supposing a form of lesion spread which is characterized by nothing but an absolute randomness -- which lesion-interpretation apparently justifies
- considering the specific patterns of, in particular, cerebral "Dawson's fingers" and spinal cord flank affections just as coincidental, and eventually
- attributing any corresponding condition to a single, essentially cryptic, systemically scattered blood-borne agent.

This vagueness about multiple sclerosis is handy: It avoids the need to differentiate observed lesion patterns and to elucidate their meaning. Together with the speculative "inflammatory demyelination" conception, the idea of "disseminated sclerosis" has thus proved pivotal in establishing multiple sclerosis - including its specific forms -- as a "cryptogenic, autoimmune disease". However, regarding the indefiniteness of these clinical, histological and pathogenic disease characterizations, it is abundantly clear that no two victims of multiple sclerosis ever necessarily suffer from one and the same disease, in terms of a definite specific injurious process.

Schelling further notes that nothing can be concluded from the presence of immunocytes near demyelinated axons as these findings are typical in other CNS injuries of vascular or mechanical origin. In regards to the CSF oligoclonal IgG bands, Schelling points out that they are neither peculiar nor specific to MS and appear in many other conditions affecting the CNS (Ref). Therefore, what is considered the most important diagnostic test for MS lacks specificity. Indeed, no reliable biomarker or diagnostic test
has ever been found for MS, a profound mark of shame for all the highly paid “experts” who live off the disease (Ref).

More criticism comes from Behan and Chaudhuri who list some facts about MS which cannot be explained by the autoimmune theory (Ref):

- Age effect of migration
- Geographic variation (higher prevalence in most northern latitudes)
- Maternal contribution to disease risk (Ref. 5)
- Early and extensive grey matter involvement (estimated number of deep grey matter lesions per gram wet weight is higher than in any other brain structure [Ref. 6])
- Progressive brain and spinal cord atrophy, beginning at the stage of clinically isolated demyelinating syndromes (Ref. 7)
- Selective anatomical localization, symmetry and sharp margins of plaques
- Absence of specific immunological marker
- Effect of stress
- General failure of immunotherapies that are highly successful in other organ-specific autoimmune diseases and transplant rejection
- Associations with Charcot-Marie-Tooth disease and neurofibromatosis-1 (Ref. 2)

On the other hand, the biomechanical model postulated here will specifically account for nearly all of the above findings regarding MS.

During the 1930s, there was a debate between Putnam and Thomas Milton Rivers of the Rockefeller Hospital on the cause of MS. Between 1910 and 1935, more than half of all US medical schools merged or closed, consolidating control into a small, elite, legally-privileged doctor class. At the tail end of this consolidation which inherently promoted group-think, Rivers published three studies in 1933, 1934, and 1935 that absurdly equivocated MS with experimental autoimmune encephalomyelitis (EAE). In doing so, he laid the necessary groundwork for a decades-long wild goose chase at incalculable human and financial cost. Wootla et al sum up the fruitless and ridiculous endgame of the EAE model,

Many of the observed findings have subsequently led investigators to false conclusions regarding MS pathogenesis. Immune cells are present in the MS plaque, and the immune system is important in the pathogenesis of the disease because a number of immunomodulatory and immunosuppressive therapies do decrease relapses and the number of gadolinium-enhancing lesions in MS brain. However, the long-term consequences of immunosuppression on disease course are unknown because most published clinical trials end after two years of observation, an insufficient period of time to address the long-term consequences of these treatments. It is increasingly evident that CD8+ T cells and their effector molecules may directly affect the disease process. Unfortunately, despite years of documentation of involvement of CD8+ T cells in MS lesions, scant experimentation has been performed on this aspect of the immune response. This is probably due to the bias of the experimental model, EAE, in which CD8+ T cells play only a regulatory role whereas CD4+ T cells play a major effector role in disease pathogenesis. Once we move away from the experimental model and begin to investigate MS in
humans, it becomes apparent that the MHC class II CD4+ T-cell immune response yields less important critical data of the MHC class I CD8+ T-cell immune response. The most important diagnostic test for MS continues to be the presence of increased CSF IgG and the presence of specific oligoclonal bands in the CSF but not in the serum. Therefore, it is critical to identify the specificity of these bands. Ultimately, it may be proven that CSF oligoclonal IgG bands play a neuroprotective rather than a pathologic role [137–140].

In the face of overwhelming evidence (or lack thereof), the autoimmune paradigm is in its death throes. At this stage, Schelling raises the pertinent question,

In view of the given facts we must ask ourselves whether the MS patient's shameless exploitation for an as senseless as profitable drug experimentation, grounded in an illogical MS "definition" and "identification", does not form an ethical issue.

Nevertheless, a revamp of CSF and ISF physiology will be the starting point for a sweeping reappraisal of MS.

**Adopting a Sensible CSF Physiology**

Despite advances in medical imaging, some of the most fundamental tenets of CSF physiology remain in question such as the mechanisms responsible for CSF production and absorption. Consequently, our understanding and effective treatment of diseases that involve a breakdown of the cerebral windkessel mechanism have been substantially delayed. A windkessel is any system that transforms pulsatile flow into steady flow. In the case of the brain, the CSF and vascular systems interact with the brain tissue in a complex manner to transform the incoming bolus of arterial blood during systole into nearly steady blood flow at the capillary level.

There are generally two schools of thought on CSF physiology, the classic bulk flow model and the hydrodynamic model. In the classic bulk flow model, most of the CSF is produced by the choroid plexus, flows through the ventricular system into the subarachnoid space, and is eventually reabsorbed into the dural sinuses via arachnoid granulations. In the hydrodynamic model, the CSF is locally produced and absorbed by the brain capillaries (and possibly the spinal capillaries). Thus, the CSF and cerebrovascular systems are intimately related in this model which is evidenced by their complex interplay during the intracranial windkessel effect. The hydrodynamic model constitutes a vast departure from the bulk flow model and a paradigm shift is emerging in hydrocephalus research (Ref). Bergsneider and others have noted that the bulk flow model is overly simplistic, potentially misleading, and unable to explain the pathophysiology of communicating hydrocephalus,

If communicating hydrocephalus were truly caused by an increase in the CSF outflow resistance at the arachnoid granulations, then one would expect an increase in the pressure gradient between the pressure in the subarachnoid space and the sagittal sinus venous pressure. An increase in this pressure gradient has yet to be convincingly demonstrated (10, 29). Even the etiology of obstructive hydrocephalus, in classic first-order thinking, must be questioned. Tisell et al. (30) demonstrated that, in adult patients with documented aqueductal stenosis (complete
obstruction), there was no difference in pressure and CSF outflow resistance between the ventricular system and the subarachnoid space.

Where did things go wrong? Past experiments used macromolecules to study CSF volume hydrodynamics. Due to the different fate of macromolecules and water within the CSF, the results were misinterpreted to support the notion of bulk flow. More recent experiments using 3H-water to study hydrodynamics depict an entirely different picture of CSF flow. Klarica et al summarize the findings as follows (Ref).

Based on our experimental results and literature data, we proposed a new hypothesis ("model") of CSF physiology [6]. We wish to emphasize that our hypothesis is based on more than thirty years of continuous experimental research. According to our hypothesis, CSF is not being actively produced predominantly by choroid plexuses, and does not flow unidirectionally to cortical SAS to be passively absorbed through arachnoid villi. This means that CSF is being permanently produced and absorbed inside the entire CSF system, as a consequence of water filtration and reabsorption through the capillary walls into the interstitial fluid (ISF) of the surrounding brain tissue, which was thoroughly explained in our paper [5,6,12]. In brief, it was demonstrated that water passage between cerebral capillaries and ISF is relatively free [13,14], while the passage of proteins and inorganic electrolytes is greatly restricted. Our results obtained on cats show that during slow infusion into the lateral ventricle, 3H-water reached a concentration several times higher in the plasma at the confluence of the sinuses than that in cisternal CSF and arterial plasma [5]. Thus, it appears that 3H-water is absorbed from the brain ventricles into periventricular capillaries which drain into the confluence.
These findings are in agreement with other investigators over the years who proposed that cerebral capillaries are primarily responsible for absorbing CSF (Ref, Ref, Ref, Ref, Ref). Given the nature of the absorption and filtration of CSF/ISF, the entire system functions like a closed container which in turn encloses the brain and spinal cord with continuous, global fluid turnover. Bulat et al. concluded (Ref),

Our results support the idea that CSF system functions like a closed box which operates via ISF and cerebral microvessels: the volume of ISF and CSF is continuously formed by water filtration from arterial capillaries and reabsorbed in venous capillaries and postcapillary venules so that the volume of ISF and CSF is constantly renewed. Water, which constitutes 99% of ISF and CSF volume, does not flow unidirectionally along CSF spaces but is locally formed and reabsorbed.

Absorption and filtration at the capillary level is governed by the Starling equilibrium. Klarica et al elucidate the process,

Water passage between cerebral capillaries and ISF is relatively free, while the passage of proteins and inorganic electrolytes is greatly restricted. Since proteins and electrolytes contribute 0.4% and 94%, respectively, to total plasma osmolarity, it has been recently proposed that electrolytes, mostly Na and Cl which contribute 83% plasma osmolarity, are main regulators of water filtration and reabsorption. During water filtration in arterial capillaries under high hydrostatic pressure, the electrolytes are sieved (retained) so that plasma osmotic counterpressure is generated due to water loss. This osmotic counterpressure rises along the length of capillary and when it reaches the level of capillary hydrostatic pressure, water filtration is brought to a halt. However, when such hyperosmolar plasma reaches venous capillaries and postcapillary venules in which hydrostatic pressure is low, osmotic counterpressure is
instrumental in osmotic water reabsorption from the ISF so that osmotic counterpressure is dissipated. Thus, a continuous and rapid turnover of water volume across microvascular walls occurs: filtration in arterial capillaries and reabsorption in venous capillaries and postcapillary venules.

The classic Starling equation reads as follows:

\[ J_v = L_p S \left( \left[ P_c - P_t \right] - \sigma \left[ \pi_p - \pi_t \right] \right) \]

where:

- \( J_v \) is the trans endothelial solvent filtration volume per second (SI units of \( \text{m}^3\text{s}^{-1} \)).
- \( [P_c - P_t] - \sigma [\pi_p - \pi_t] \) is the net driving force (SI units of Pa = \( \text{kg m}^{-1}\text{s}^{-2} \), often expressed as m\( \text{Hg} \)).
- \( P_c \) is the capillary hydrostatic pressure.
- \( P_t \) is the interstitial hydrostatic pressure.
- \( \pi_p \) is the plasma protein oncotic pressure.
- \( \pi_t \) is the interstitial oncotic pressure.
- \( L_p \) is the hydraulic conductivity of the membrane (SI units of \( \text{m}^2\text{kg}^{-1} \), equivalent to \( \text{m}^2\text{s}^{-1}\text{mmHg}^{-1} \)).
- \( S \) is the surface area for filtration (SI units of \( \text{m}^2 \)).
- The product \( L_p \cdot S \) is defined as the filtration coefficient (SI units of \( \text{m}^3\text{s}^{-1}\text{kg}^{-1} \), or equivalently in \( \text{m}^3\text{s}^{-1}\text{mmHg}^{-1} \)).
- \( \sigma \) is Staverman's reflection coefficient (adimensional).

In addition to fluid absorption and filtration, the elastic mechanics of the spinal CSF system need to be understood and appreciated. Klarica et al summarize the literature on the significant distensibility of the spinal thecal sac (Ref).

Previous models of CSF system consisted of a rigid long tube closed from either both or one end by distensible materials (12). Such models failed to recognize main biophysical differences between the cranial and the spinal part of the CSF system in vivo. It is known that, in contrast to the cranial part, the spinal part can significantly change its volume (13-15). In the cranial cavity, the dura mater is closely connected to the bone, so cranial subdural space cannot change its volume. On the other hand, the spinal dura is only partly attached to the vertebral column, while its largest part is separated from the vertebrae by epidural space filled with fat tissue and venous plexuses. Thus, the spinal subarachnoid CSF space can expand or contract (13-15). For example, changes of CSF volume in the lumbar subdural space can be recorded during various physiological maneuvers (16), including increased pressure on the abdominal wall (17). Such changes of subdural volume are primarily enabled by the rich venous plexus in the epidural space, which can be filled or emptied depending on the exposure to various pressures (18,19). Magnetic resonance imaging shows that thoracolumbar CSF volume can be changed by 40%, depending on abdominal pressure: increased abdominal pressure leads to accumulation of venous blood in the epidural plexus and increase in the blood pressure, and consequently to the
decrease in the thoracolumbar CSF volume (17). The spinal dura is stretched to a maximum in longitudinal direction, but it can be distended in perpendicular direction due to the arrangement of its elastic and collagen fibrils (9,10). The spinal CSF space can compensate for 30-80% of cranial pressure increase, as in case of brain edema, bleeding, tumors, or hydrocephalus, because of the distensibility of spinal dura and CSF displacement from cranial to spinal space (20,21). Thus, our model with the distensible spinal part and non-distensible cranial part seems to mimic faithfully the situation in vivo in cats.

Starting with these physiological facts, a more complex model has been proposed for intracranial hydrodynamics. Citing the work of Egnor et al., Bergsneider explains the emerging new theory of the CSF system’s purpose,

Egnor et al. (8–10) have elegantly suggested that the function of CSF system is to tune the primary harmonic resonance of the intracranial compartment to optimize the intracranial Windkessel phenomenon. Theoretically, a tuned oscillator could reduce the impedance mismatch by shifting the fundamental harmonic resonance frequency of an object while dampening high-impedance resonant frequencies.

A mechanical equivalent of oscillating systems has been classically illustrated using a weighted block suspended from a spring. Stimulating the system at the fundamental harmonic frequency would result in wild, destructive oscillations of the block. With regard to blood flow physiology, the vasculature and its surrounding tissue is the “block” that is being stimulated by a pulsatile blood flow input. If this input were to occur at the natural harmonic frequency of the system, then the fragile capillary system might experience bounding blood pressure fluctuations.

One approach to minimize large capillary pulse pressures would be to place a damper on the system (analogous to a shock absorber used in automobiles). Dampers, however, absorb energy and, therefore, reduce the efficiency of energy transfer. In effect, vascular autoregulation is a feedback-controlled damping system that regulates the pressure drop over the arterial tree by either vasodilation or vasoconstriction of arterioles.

A different, more efficient, approach to counteract a potentially harmful stimulation at the fundamental frequency would be to add a tuned oscillator. When a properly chosen smaller weight and spring is attached to the original block suspended from a spring, the smaller block will vibrate in such a manner that the movement of the original larger block will be minimal. In the second-order hemodynamic model discussed here, the second block and spring is anatomically represented by the CSF system and the distensible spinal dura.

The CSF system is the most logical intracranial component comprising the (presumed) tuned oscillator. The complex, dynamic movement of CSF both within the cranium and to-and-from the spinal compartment could provide optimal impedance matching between the intracranial compartment and the cerebrovascular input. Similar to the added mass and spring, the CSF system has an inherent mass (because of its volume) and elastance (because of the recoil offered by the distensible spinal dural sac). From a teleological perspective, the CSF tuned
oscillator is probably broadly tuned around the resting heart rate frequency. Deviations from
the resting heart rate will result in incremental increases in the cerebrovascular reactance. Fine-
tuning of the amount of CBF (cerebrovascular autoregulation), however, likely occurs at the
arteriolar level by adjustments of cerebrovascular resistance. For example, an increase in
cerebrovascular reactance could be compensated by a reduction in resistance, thereby
maintaining a constant cerebrovascular impedance. As a result, cerebrovascular impedance can
be maintained within a narrow range to maintain a constant CBF.

Lastly, the hydrodynamic model revamps the physiology of ICP. Bergsneider elaborates,

Given these considerations, the physiological definition of ICP must be precise. For the purposes
of this second-order model, ICP will be equated to intraparenchymal pressure. Intraventricular
and subarachnoid pressure will be considered separately. In practicality, pathological
perturbations to the system generate brief net pressure gradients that likely dissipate once a
new equilibrium state is reached. Therefore, the analysis of pressure gradients between
subcompartments is important to the understanding of how the system changes. Once (if)
equilibrium is reached, the net pressure gradients will again be zero. An additional consideration
is that there is evidence that intraventricular CSF communicates with the parenchymal
extracellular fluid (18, 28). Flow of CSF between these subcompartments likely occurs normally
and may be enhanced in pathological situations.

As proposed, the mechanical containment of intraluminal cerebral capillary pressure is
considered minimal. Interstitial pressures are, therefore, regulated by the Starling Equilibrium—
a process tightly controlled by the blood-brain barrier (BBB). The difference between capillary
and interstitial hydrostatic pressures (ICP) will, therefore, be predominantly related to the
oncotic/osmotic pressure differential, which, in turn, will be a function of the BBB (within the parenchyma). Similarly, the intraventricular pressure will be primarily determined by the choroid capillary hydrostatic pressure and the state of the blood–choroid plexus barrier. A slight differential between the ventricular and brain pressures could explain a bulk flow of CSF out of the ventricles—a situation compatible with the first-order model of CSF physiology.

Given the above stipulations and definitions, ICP will mainly be a function of cerebral capillary pressure. It should be noted that this concept of ICP is significantly different from that expressed in most modern neurophysiological literature. The standard, accepted explanation of ICP, typically involves a scenario in which volume is added to the intracranial compartment. As stated previously, appreciable volume cannot be added to this compartment. Because the cranium is “leaky,” adding volume merely displaces fluid (either CSF or blood) out of the intracranial compartment. The error in reasoning occurs in the interpretation of the Langfitt pressure–volume curve. It is not the volume, per se, which causes the increase in ICP; instead, it is the force required to displace the equivalent volume from the intracranial compartment that determines the ICP. From a practical standpoint, the only such force is derived from the cardiovascular system (ignoring, for the moment, external forces, such as the impact during head injury). The only force an intracranial space-occupying lesion can exert is gravitational. We argue here that changes in ICP occur secondary to changes in capillary pressure or alterations of the BBB. Furthermore, it is proposed that intracranial space-occupying lesions interfere with cerebrovascular dynamics indirectly via obstruction of the CSF system (or alterations of the BBB).
There are three crucial takeaways from the above revision to ICP with particular relevance to understanding MS. The first is that ICP is equated to intraparenchymal pressure and that it is mainly a function of cerebral capillary pressure. Second, increases to ICP are not caused by an addition of volume per se but from the force required to dispel the additional volume. Thirdly, brief net pressure gradients are generated between intracranial subcompartments during pathological situations which is important to understanding how the entire system changes. With the crash course complete, we’re ready to get started.

**Explaining Relapse-Remitting/Secondary-Progressive MS**

**Focal Lesion Characteristics Imply a Mechanical Cause**

85% of MS patients follow the RRMS/SPMS pattern. This disease course is characterized by an initial phase consisting of acute relapses followed by a partial or complete functional recovery. Over time, the functional deficits from these relapses will accumulate and the disease enters a chronically progressive phase without relapses, termed SPMS. The peculiar brain lesions that are the classic hallmark of MS pathology mostly appear during the RR phase, are perivenous, and tend to vanish or become “silent” in the SP phase. Beginning with a rational and concrete assessment of these cerebral lesions, one can begin to trace and unravel what MS is. On MS-specific lesions, Schelling is authoritative. He writes ![Emphasis original](https://example.com)

Five features characterizing the spread of the specific brain lesions of multiple sclerosis prove useful for determining injurious impacts which cause the damages:

1. The common asymmetries of the plaque expansions away from their veins, especially in their bizarre extremes.

2. The plaques’ emergence exclusively from certain segments or even sectors of the walls of their veins.

3. The consistent countercurrent spread of damage, i.e. its progression, without exception, in a direction diametrically opposite to the normal venous (and interstitial fluid) flow.

4. The origin of lesions -- and particularly of the largest lesion formations -- preferentially from strong, i.e. thick-walled and therefore scarcely penetrable vein segments.

5. The lesion spread only along a small, select system of cerebral veins.

Following is an evaluation of each of these five key aspects of lesion genesis, especially with regard to its significance for the understanding of the disease:

1. Asymmetries in the lesion expansion, and eccentric courses of the plaque veins: Compact lesion expansions or projections mainly or exclusively to one side of a length of plaque vein, such as are typical of cerebral multiple sclerosis, require a well-directed mechanical impact that no microscopic agent could conceivably provide, especially through such strong vein walls as
have commonly been found in periventricular plaque expansions. Further explanations of the process responsible for the unique plaque projections are given below.

2. Peculiarities of the involved vein lengths: The central role of veins in the development of cerebral multiple sclerosis has mainly been obscured by the capricious eccentricities of plaque vein placement relative to lesions. The emergence of plaques only from certain sectors of the walls of their veins, which at first sight appears rather erratic, might also have contributed to the late realization of the role of veins. The expansion of brain plaques mainly from venous bends and narrowings, or from terminal venous arborizations, was in fact directly described only in 1964 by Fog (47, 48). Of particular interest here is the occurrence of analogous findings in hypertensive encephalopathy, in which areas particularly exposed to the pressure of abutting arterial bends tend to become demyelinated, or even battered out to circumscribed hollows (reminiscent of the hollows surrounding Dawson’s plaque veins) (117, 146, 163).

3. The lesion spread countercurrent to the normal venous flow direction: According to all available evidence, specific injuries to the brain consistently start out from strong proximal vein segments and then proceed for varying distances upstream. The process of cerebral multiple sclerosis thus advances in a direction diametrically opposed to that of normal venous flow. The extraordinary significance of this circumstance was already grasped by Carswell, long before the role of veins in cerebral multiple sclerosis was realized: "In inflammation the local congestion commences in the capillaries, afterwards extends to the small veins, but never to large branches; in mechanical congestion [by venous flow inversion] the blood accumulates first in the venous trunks, which are always conspicuous, and afterwards in the branches and capillaries" (24). Carswell here indicated a relationship which actually constitutes the master key to the accurate understanding of multiple sclerosis. **The advancement of the specific cerebral lesion formations of multiple sclerosis in the direction from wide vein stems upwards towards narrow venous roots shows the whole process to be essentially mechanical in nature.**

4. Primary altering of strong-walled periventricular collecting veins. Putnam and Adler's first illustrations of the plaque veins' "gnarled" look, i.e. irregular distensions and distortions (Plate VII) represent another finding awaiting its explanation in terms of mechanics. And there was one further significant finding: The maximal distension of plaque veins immediately downstream to their thrombotic obstructions and their maximal distortion downstream to other, more peripheral plaques. This included a stepwise increase in the thrombosed veins' proximal distension, in the direction of the obstruction, at each of three subsequent points of entrance of venous affluents. Comparable, though less detailed, observations made several years later underlined the necessity of providing a physical explanation for the plaque vein's distention, not upstream, but downstream to its thrombotic occlusion (38). In this connection a picture presented by Ingrid V. Allen in 1981 is especially relevant. On a cerebral hemisphere's medial aspect a number of vein-centered plaques are apparent, spread beneath the lateral ventricular wall and surging up off of the corpus callosum undersurface (3). On closer examination it can be discerned that the stem and first branches of a large ventricle vein have grooved for themselves wide beds whose breadth is nearly three times that of the involved vessels' diameters — a detail
reminiscent of Charcot’s first documentation on cerebral multiple sclerosis (Plate IV, fig. 1). Together with the findings of specific plaques rising up from strong, proximally strikingly distended veins, these observations again point to the effects of notably strong forces. It seems obvious that the necessary physical impulses must have been exerted from inside the plaque veins, i.e. they can only have been exerted by venous blood. In considering the peripheral narrowing and central widening of the venous tree, as well as the excessive rises in pressure only in the central veins, the following conclusion appears self-evident:

The specific brain plaques of multiple sclerosis can only be caused by energetic venous back-jets set in motion by intermittent rises in the pressure in the large collecting veins of the neck, but especially of the chest. Since the process of cerebral multiple sclerosis does not lead to an even distension of the proximal branches of a particular venous drainage system up to a definite length, since its plaques emerge preferentially from venous bends, narrowings and arborizations, and since the plaque expansions from veins show such striking eccentricities, the impacts of the regurgitant blood quite clearly tend to be very unevenly distributed (Plate VIII; Plate IX, fig. A). To be able to exert such effects the peripherally directed venous currents must at times attain remarkably high velocities and affect the brain in the course of very short periods of time.

5. As to the selective involvement of a definite venous drainage system in the brain: While injecting, under heavy pressure, carmine-gelatine into a human body’s straight sinus in an attempt to render its tributary veins in the cerebral hemispheres more prominent, Benno Schlesinger, in 1939, came unawares very close to explaining the cerebral multiple sclerosis lesion's genesis. He realized that extravasations produced around the lateral ventricles' outer angles (Steiner's "Wetterwinkel") "closely simulate the distribution and even the shape of plaques in advanced cases of multiple sclerosis" (121). In this way, Schlesinger, an expert on cerebral vascular anatomy, clearly demonstrated that the most prominent plaque veins represented the main affluents of the straight sinus. The fact that other affluents of the straight sinus, i.e. veins of the 82 brainstem, must equally be considered as classic plaque veins appears to have been noticed only by Lumsden, in 1970 (71).
Schelling makes an air-tight case for the mechanical genesis of cerebral lesions. Their anatomical localization, peculiar dimensions and appearance, and retrograde pattern of spread can only rationally be accounted for by powerful venous reflux into cerebral veins. Schelling identified the straight sinus as the primary route of the reflux and further noted its functional isolation.

The remarkable functional isolation of the straight sinus system of venous drainage has been consistently illustrated not only anatomically (9, 120), but also - more dramatically -- in the literature on the disastrous effects of (especially thrombotic) straight sinus occlusions. The evidence presented demonstrates that, if the venous outflow through the straight sinus is blocked, the collateral venous drainage from the brain's central parts tends to decompensate under the mere perfusion load of blood circulation (10, 14, 54, 129, 149, 150, 151, 156). It becomes clear that the potentially far more massive overloading of the straight sinus affluents by intense venous back-jets can certainly not be expected always to be dissipated in a harmless fashion.
A force chronic and powerful enough to generate the necessary pressures and velocities to create such lesions was necessary. Schelling posited that an incompetent internal jugular vein (IJV) valve could allow venous reflux up from thoracic veins under certain circumstances. Mechanical impacts to the torso can shift significant quantities of blood but in reality probably lacks the chronicity to factor significantly in any given MS case. Remarking on the explanatory difficulties of acute changes in central venous pressure causing cerebral MS lesions, Schelling writes,

Apart from their typically being limited to affluents of the straight sinus, the brain plaques of multiple sclerosis expand from only certain small section(s) of a plaque vein's surface. The question arises as to what may limit and localize the particular venous regurgitation effects. A consideration of the acute, both absolute and relative rises in intra-abdominal and intra-thoracic pressure reveals the existence of a number of factors which can limit a spread of venous regurgitation into particular cerebral veins. The primary limiting factor against a strong retrograde venous invasion of a particular part of the brain lies in the rapidity with which the thrust of any correspondingly localized venous regurgitations is counterbalanced by separate competing venous regurgitant and ordinary arterial flows into the craniovertebral space. A regurgitation into particular cerebral veins may also end precipitously, due to an exhaustion of its own volume or, in cases involving a larger intracranial venous domain, because the veins providing for a venting of the craniovertebral space are emptied too quickly. Finally, the ordinary course of trans-diaphragmatic pressure gradients makes it probable that venous regurgitations into the brain will often be stopped by competing venous back-jets from intra-abdominal collecting veins into the epidural vein plexus of the lower spinal canal.

The general problem with thoracic reflux causing the spread of cerebral lesions is that there are too
many potential counterbalancing forces in play. Even if pressures and volumes are sufficient or if one of the IJV valves is particularly incompetent or absent, the design of the dural sinuses is such that unilateral IJV reflux will harmlessly descend back down the contralateral IJV (Ref). Cerebral MS lesions are clearly mechanical in origin yet the majority of the body’s venous blood volume is not liable to be behind their spread. Appreciation of this conundrum implicates the comparatively paltry volume of blood above the level of the IJV valves as being responsible, however difficult to believe at first thought. The only conceivable force in the region capable of generating bilateral and simultaneous reflux in the IJVs is the human jaw and cranial bones.

The Focal Lesion Generating Mechanism

The discovery of hypermobile cranial bones in MS patients was a breakthrough to unraveling one of the essential causes of MS. Williams et al observed that during sustained teeth clenching of 100 pounds of force, the real-time lateral temporal bone displacement is six times greater in MS patients than controls (mean 1.71mm vs .27mm). It should be noted that nocturnal clenching forces can easily exceed 300 psi, with reports as high as 2000 psi at the back molars. Williams et al explain the novel testing protocol used in the experiment,

The technique provided high-resolution measurements of the change in the position of the echo from the initial estimate. For these tests, the position of three echoes was tracked with the PPLL: an echo from the transducer’s surface at the skin; an echo from the endocranial surface of the right temporal bone just as the signal entered the cranium (Echo 1); and an echo from the endocranial surface of the left temporal bone after the signal had passed through the cranial cavity (Echo 2). After tracking changes in the position of these echoes with time, the data were saved to a file. By subtracting the difference in the position between Echo 2 and Echo 1, it was possible to measure changes in the width of the intracranial distance between the two temporal bones, eliminating dimensional changes due to the motion of the temporal muscle during clenching. This value is the intracranial length or distance between the inner tables of the temporal bones (derived from the change in acoustic wavelength, ∆L). In essence, the PPLL tracks changes in the distance between the transducer, the proximal (right) and the distal (left) intracranial wall. To subtract out soft tissue movement between the transducer and the proximal wall, the saved data were reprocessed, this time locked on the echo from the proximal wall (Echo 1). By subtracting the second result (Echo 2) from the first, the authors were able to monitor changes in the distance between the proximal and distal temporal bones during clenching. For tests of reproducibility, one subject was chosen at random. Thirteen tests and data points were obtained. The data are displayed in Table 2 with statistical analysis in Table 3. The results of the reproducibility test showed there was no statistical difference in the measurement procedure. Therefore, analysis of variance (ANOVA) was used on the data obtained from the control subjects and MS patients who participated in this study.
Bilateral displacement of the temporal bones is possible due to the unique design of the squamosal suture. In contrast to other sutures, the squamosal suture is beveled and smooth similar to a gliding joint and serves as the attachment point of powerful jaw muscles. Under mechanical load from the jaw, the temporal bone is tractioned caudally and laterally. The squamosal suture does not fuse completely until after 70 years of age (Ref) and follows a highly irregular pathway to fusion (Ref). Rajitha writes,

Proximity to biological features like muscles has been shown to alter the route of synostosis, like the masseter muscle and the squamosal suture (Kokich, 1976). Here, the suture followed a highly irregular pathway to fusion, indicating that the presence of the muscle and the biomechanical forces associated with mastication influenced the rate of progression. A similar structural set-up around other sutures may explain why variability is the norm for cranial sutures.

It should be observed that the typical age range for developing MS is 20-50 years of age. Individuals who develop MS after 50 years of age typically develop PPMS. As will be further elucidated, PPMS is a related but distinct biomechanical disease that is less dependent on substantial cranial bone movement and more dependent on cranial morphology with other synergistic factors. The risk for developing RRMS falls as the cranial sutures fuse completely with age.

Hubbard et al determined that the strength of the cranial sutures is generally as strong as layered cranial bone of the same thickness, leading Williams et al to hypothesize that a vitamin D deficiency in genetically susceptible people may cause a reduction in the layered cranial bone, thus rendering the cranial sutures more compliant (Ref). Extending their results, it was hypothesized that a sustained episode of bruxism (that can last up to 45 seconds) could temporarily expand the intracranial space causing a sustained drop in ICP. Since venous blood vessel compliance is 10-20 times greater than
arterial blood vessel compliance for low ICP, a substantial volume of blood could accumulate in the cerebral veins during this period.

While supine, extracranial venous drainage is normally through the IJVs which contain a valve just proximal to their ends at the subclavian veins. The valves are designed for relatively low-pressure blood flow leaving the cranium propelled along with minimal accelerative force by the windkessel mechanism. Therefore, when the jaw clenching ends and the cranium contracts, the accumulated volume of blood is accelerated out under pressures and velocities exceeding the limitations of the IJV valves. When fluid travelling in a pipe strikes a barrier, a rebound wave is generated (Ref):

> When the leading edge of a water column strikes the closed valve it comes to a halt, but the water behind it is still in motion and, since it has nowhere to go, it begins to compress. This compression along the entire length of the column allows a small amount of water to continue to flow into the pipe even though the leading edge has halted. When flow ceases, its kinetic energy of motion and that due to compression is transformed into pressure and energy is conserved. Compression begins at the leading edge of the water column and since the additional energy it produces cannot continue on past the closed valve, a pressure or shock wave is generated and travels back upstream.

When the vented blood strikes the IJV valves, simultaneous rebound waves will travel up the IJVs, dural sinuses, straight sinus, and eventually the vein of Galen and its tributaries, thus creating the characteristic perivenous lesions by mechanical impacts and stretching of vein walls. The trauma causes an inflammatory breakdown of the blood-brain barrier (BBB), edema, and the immune cleanup response thought to be the cause of MS. There are numerous pathological changes in MS consistent with an event like this occurring chronically such as diffuse global brain damage, periventricular atrophy, perivenous...
lesion spread, and altered collagen expression in the IJVs. Incompetent, thickened, or irregular IJV valves could present a more robust barrier to venous evacuation thus generating more powerful rebound waves back into the intracranial space.

Another possibility meriting consideration is that the dural sinuses could be compressed by the brain from above during the cranial contraction. A similar phenomenon involving compression of the dural sinuses by the brain has been postulated as a catalyzing mechanism in idiopathic intracranial hypertension (IIH). IIH will be discussed in more depth later. In this scenario, it is conceivable that the volume of blood attempting to suddenly egress through the constricted dural sinuses is too great, resulting in venous flow reversals and even deep flow rerouting to the auxiliary venous plexuses. If such compression occurs, at a minimum, constricted dural sinuses will increase pressures and velocities of the venous pathway stretching from the straight sinus to the the internal jugular vein valves.

Many of the severely atrophic regions in RRMS/SPMS correlate with the choroidal drainage route including the lateral ventricles, the third and fourth ventricles, the caudate nucleus, and the corpus callosum. Significant periventricular atrophy and ventricular enlargement also occurs in early RRMS patients (Ref). A review of the venous anatomy draining the choroid plexus will help elucidate the mechanisms behind these specific clinical changes. From “The Choroid Plexus in Health and Disease” (Ref),

The choroidal veins drain the lateral and 3rd ventricular plexuses. They subsequently unite with the terminal veins lying beneath the ependyma between the thalamus and caudate nucleus, and
with the thalamostriate veins in the region of the interventricular foramen to form the internal cerebral veins, the small veins of Galen. Two internal cerebral veins course posteriorly in the roof of the 3rd ventricle; they join in the region beneath the splenium of the corpus callosum to form the great cerebral vein of Galen. The latter then empties into the straight sinus. Occasional veins from the glomus may drain directly into the internal cerebral veins. Some veins draining the portion of the choroid plexus lying in the inferior horn of the lateral ventricle may open in the basal vein. The choroidal veins from the plexus of the 4th ventricle drain into the basal veins. The latter are formed by union of the anterior cerebral vein and the deep middle cerebral vein in the region of the anterior perforated substance. The basal vein passes posteriorly around the cerebral peduncle, and terminates in the great cerebral vein.

Early in the RRMS stage, there is a more particular distribution of pathologically-enhanced pressure gradients between subcompartments, particularly between brain tissue and venous vasculature. These are the regions where the brain will typically undergo the greatest degree of volume change. Due to the subarachnoid location of many cerebral arterial vessels and the mostly steady flow in cerebral veins, the brain usually does not experience substantial changes in volume. Thus, when the cranium contracts, perivenous regions are pushed inwardly that meet an outwardly-directed hydrostatic force from refluxing blood. Mechanical synergy substantially intensifies compression of adjacent tissue structures. Engorgement of the straight sinus will exert an upward-rearward force on the occipital lobe and a downward force on the cerebellum while the dural sinuses will exert an upward force on adjacent cerebellar structures. Repetition of these forces throughout the disease course explains progressive pericerebellar atrophy, cerebellar dysfunction, and occipital cortex atrophy observed in the RRMS/SPMS pattern (Ref).
What causes the ventricular enlargement? In the hydrodynamic model, intraventricular, subarachnoid, and intraparenchymal pressures are considered separately. The intraventricular pressure is mainly determined by the choroidal capillary hydrostatic pressure and the state of the blood-choroid plexus barrier. Since the choroidal plexus epithelial layers don’t have an elastic or muscular layer, the choroidal capillary hydrostatic pressure is linearly related to the intraventricular pressure. When clenching ceases and the cranium contracts, the cranial bones deflect causing an inwardly-directed pressure wave through the brain tissue directed at the ventricles. Concomitantly, blood will be propelled retrogradely towards periventricular veins and capillaries adjacent to the choroid plexus. When the choroid capillary hydrostatic pressure spikes, the intraventricular pressure spikes as well, generating an outwardly-directed pressure wave through the brain tissue. Once again, mechanical synergy causes profound compression of the periventricular tissue leading to rapid atrophy and ventricular enlargement. To review, there is a brief pressure gradient generated between the subarachnoid space and cerebral cortex (grey matter atrophy from onset), then a continued inward gradient through the parenchymal tissue (diffuse white matter damage), a marked gradient between the venous drainage routes and the perivenous tissue (perivenous focal lesions, enlarged perivenous spaces), and another major gradient in an outward direction at the periventricular border (periventricular atrophy, ventricular enlargement).
The increase to ICP during cranial contraction will be equal to the force necessary to discharge the additional volume of blood for the case-specific hydrodynamic parameters. Cerebrovascular impedance is the algebraic sum of cerebrovascular resistance and cerebrovascular reactance. Blood flow inertial reactance is normally low due to the windkessel mechanism. In this case however, inertial reactance would be greater than normal since much of the accumulated blood is pooled near standstill following a period of low ICP. The subsequent venous reflux causes mechanical stretching and damage to vein walls which leads to endothelial dysfunction (Ref, Ref, Ref). Endothelial dysfunction is known to increase vascular resistance which accelerates disease progression, at least in part, by incremental increases to cerebrovascular resistance (Ref). Obstructions to CSF pulsations at the craniocervical junction will redistribute force (derived from the resistance) to cerebral capillaries and ultimately to intraparenchymal pressure (ICP).

Bulat et al showed that fluid injected into the ventricles under normal conditions was rapidly absorbed by transventricular microvessels. Substantial transependymal migration of CSF probably only occurs when an outward pressure gradient at the periventricular border exists, such as during a sustained increase in ICP (Ref). MRI evidence from Fonar Corporation shows CSF “leaking” from a ventricle and communicating with a nearby lesion (Ref), confirming that transventricular CSF flow occurs and is enhanced during pathology. Chronic but temporary spikes in intraventricular pressure could cause the fluid to be forced through the ependyma itself, alongside transependymal vessels, or from hemorrhage of these vessels. Whatever the cause, the extracellular fluid would take the path of least resistance and flow into the perivascular Virchow-Robin (VR) spaces. Damadien et al write,

In addition, the peri-ventricular distribution of MS lesions naturally gives rise to the question that if MS lesions are not correlated in any way to CSF hydrodynamics, why are they not
randomly distributed throughout the white matter of the brain, instead of being clustered around the ventricles of the brain. Further consistent with the possibility that MS plaques originate as CSF “leaks” secondary to trauma, is the existence of Dawson’s fingers (Figure I) where the “long axis of the (MS) plaque” is “parallel with the white matter fibers in the corona radiata”, i.e., not within the white matter fibers themselves but parallel to them. “Dawson’s fingers” might well be the “leak” pathways of cerebrospinal fluid originating in the ventricle and joining the body of the MS plaque within the brain parenchyma. Parallel to the white matter fibers would be the path of least resistance for “leaking” CSF to diffuse within the brain parenchyma, i.e., alongside the white matter fibers.

It is important to observe that enlarged VR spaces and “black holes” are a hallmark of mild TBI and a sensitive indicator of cerebral microvascular disease (Ref, Ref, Ref, Ref). Since MS is a form of chronic but mild TBI in this model, there are quite a few similarities between MS and TBI. For example, MS patients have similar vascular autoregulatory and CBF changes to TBI patients during working memory tasks (Ref). VR spaces are likewise larger and more numerous in MS patients (Ref, Ref, Ref, Ref). Diffuse axonal injury (DAI) from TBI is well documented and DAI is increasingly being recognized as a major component of MS and is present from the onset of disease (Ref).

The TBI-like nature of MS also makes it an unpredictable and potentially life-threatening condition. In some cases, catastrophic onset of MS is an unfortunate possibility within the biomechanical framework. The case-specific conditions in these so-called “tumefactive” MS patients resulted in profound axonal injury with secondary edema, ischemia, and cerebral infarction as compared to typical MS cases. When this occurs, an MS patient is virtually indistinguishable from a severe TBI or stroke patient. Ernst et al report on a tumefactive MS case (Ref),
Structural and physiologic MRI were performed after subacute onset of left hemiparesis in a patient with MS. MRI showed a large ring-enhancing lesion with surrounding edema and mass effect; differential diagnosis included a neoplasm or a large MS plaque. Physiologic MRI showed reduced blood flow and magnetization transfer, as well as increased diffusion, in the large lesion. Because these findings suggested a tumefactive MS plaque rather than a neoplasm, the patient received steroid treatment for acute MS exacerbation. Three months later the patient improved clinically and on MRI.

The resulting edema causes a substantial maldistribution of CSF pulsations which can mimic the effect of a neoplasm. It is not readily apparent what causes such cases but the possibility of arteriovenous malformations or a particularly predisposed cerebral venous architecture should be considered. MS can also directly cause death in both young and old patients often due to brainstem lesions (Ref).

Optic involvement in MS can vary anywhere from permanent and complete blindness to an increased presence of “floaters” in the vitreous fluid. Understanding the anatomy of the eyes and optic nerves explains the near inevitability of some optic involvement in MS. Allingham et al write,

The development of the optic vesicle begins at day 22 with an evagination from the wall of the diencephalon, which creates the optic vesicle. The optic vesicle invaginates and forms the optic cup and the optic stalk. The cavity of the optic stalk is eventually filled with the axons of the retinal ganglion cells as well as the retinal vessels. The optic nerve, of course, is an extension of the central nervous system, and as such is invested by the meninges. The optic nerve, as it exits the eye, is enclosed in dural, arachnoid and pial sheaths, as well as the circulating fluid of the central nervous system, the cerebrospinal fluid (CSF). The CSF originates in the choroid plexus within the third, fourth, and inferior horn of the lateral ventricles, and drains into the arachnoid villi of the cerebral venous system, as well as through lymphatic channels. The fluid flows freely throughout the neuraxis within the subarachnoid space, which includes the optic nerve.
Acute optic neuritis (ON) appears in at least 50% of MS cases during the disease course and is the presenting symptom in about 20% of cases. The most likely cause of acute ON in MS is due to direct compression of the optic nerve by the brain. The diameter of the optic nerve sheath has been observed to decrease during CSF hypovolemia (Ref). Given that an acute endocranial expansion functionally induces CSF hypovolemia, one could hypothesize that the brain will initially sink in the cranial vault when clenching begins. When clenching ceases, the brain will once again be forced caudally within the cranial vault. Depending on the case-specific anatomy and particular forces involved, the caudal displacement of the brain may be sufficient to directly compress the optic nerve sheath resulting in acute ON. If the expansion is markedly asymmetrical, displacement of the brain would likewise be asymmetrical which would explain frequent unilateral ON. Asymmetrical symptomatology is more common in the RRMS/SPMS pattern due to the inherent volatility of the disease mechanism whereas the pattern of symptoms and damage is more consistently bilateral in PPMS which features a more uniform and subtle disease process.
Chronic cranial bone movements that generate abnormally high CSF pressures in and around the optic canal are liable to eventually cause degenerative changes. Indirect traumatic optic neuropathy causes a thinning of the RNFL due to a temporary spike in fluid pressures surrounding the optic nerve (Ref). Similar axonal loss and thinning of the retinal nerve fiber layer (RNFL) has been observed in MS patients (Ref). In obesity associated IIH, chronically increased CSF pressures are sufficient to transmit mere cardiovascular forces to cause damage (Ref, Ref). Therefore, the very high incidence of optic involvement in this model of MS is both expected and accounted for.

Looking outside of the cranium, the IJVs are the primary drainage route during sleep and experience most of the turbulent reflux. Altered collagen expression usually associated with chronic venous disease has been found in MS patients’ IJVs (Ref). The IJVs showed focal thickening of the wall characterized by collagen III fiber accumulation and support the presence of chronic venous reflux in the IJVs. Even if some of the flow reversals are not able to reach the cerebral veins to cause damage, they will surely subject the IJVs to some degree of mechanical stretching and scarring. Venous hemodynamic abnormalities in the IJVs are most severe in the region of the IJV valves in MS patients (Ref). This is the region where the IJV walls would experience the greatest mechanical stresses and hemodynamic dysfunction could expectedly be most severe here.

According to POUISselle’s Law, vascular resistance is proportional to the length of the vessel and inversely proportional to the fourth power of the radius. Similarly, blood pressure and velocity vary inversely with the cross-sectional area of a blood vessel. Therefore, a multitude of factors reducing IJV diameter could increase MS risk, worsen the ICP change during jaw clenching, and aid the focal lesion generation process. Examples include compression by the transverse process of the atlas, hypoplastic foramina, and muscular compression of the IJV (Ref, Ref). Turning of the head causes torsion and
compression of the ipsilateral IJV, thus sleep position could be acting synergistically with bruxing to generate lesions.

**Conversion to SPMS**

SPMS is recognized by most as a continuation of the same disease, only a different phase. In the biomechanical model this is also true, except that it provides a straightforward explanation for the apparent transition in disease behavior. In the biomechanical framework, SPMS is more about understanding how the system changes over time rather than introducing new disease mechanisms. As mentioned, over the course of the RRMS/SPMS disease process, pressure gradients will tend to become more uniform between the intracranial subcompartments. Therefore, there is a greater destruction of axons distal from the periventricular and perivenous regions as the disease progresses. Grossman et al report (Ref),

Although CSF volume and percentage of brain parenchymal volume both showed a strong correlation with T2 lesion volume (positive and negative, respectively), they showed a stronger correlation with peak height of the histogram. Loss of parenchymal volume in MS most likely reflects a combination of pathologic processes, including demyelination, gliosis, and neuronal loss. The net effect of these pathologic processes results in loss of brain parenchyma. FSE T2-weighted MR imaging is sensitive only to the areas of macroscopic disease. There is evidence to suggest that magnetization transfer imaging can detect macroscopic and microscopic disease as well as neuronal loss (12–15, 46). The increased sensitivity of magnetization transfer imaging as compared with FSE T2-weighted imaging results in superior correlation of the peak height of the MTR histogram with global volume loss. This finding supports the hypothesis that the MTR histogram may offer a better quantification of total disease burden in patients with MS than provided by volume measurements on FSE T2-weighted images.
The peak height of the MTr histogram is believed to be inversely correlated with the percentage of diseased brain tissue. The lower the peak height, the more globally involved the brain is in the disease. SPMS have a lower average histogram than RRMS patients (Ref). MTr provides a better measurement of disease burden than T2 lesion load given that MS is a true global brain disease.

**Fig 1.** MTR histograms in a control subject (thin line) and a patient with MS (thick line). MTR values are displayed along the x-axis and normalized pixel counts are displayed along the y-axis. The peak height of the histogram (the MTR value with the largest normalized pixel count) is decreased in the MS patient as compared with that of the control subject.
Why do the focal lesions that dominate the RRMS stage tend to disappear or become inactive or silent in SPMS? The focal lesions are a secondary phenomenon caused by global episodic ICP spikes and shearing injuries, and are typically generated following sustained drops in ICP. On a long enough timeline, the conditions and forces by which they manifest tend to exhaust and limit themselves. Schelling writes,

> The factors which limit the specific plaque spread everywhere within a sharply punched out front have never been plausibly accounted for. And yet, we have now become acquainted with many revealing details. The following relationships appear of basic significance:

- The compact massiveness of major "Dawson's fingers" or "Steiner's splashes" indicates that the thrust of the regurgitant blood is not simply exhausted by friction-induced vascular resistance.

- Nevertheless, "plaque borders" forming a series of thin, outwardly pointing epiventricular lesion spikes -- as they would be expected to be brought about by a corresponding series of regurgitant blood columns' deceleration tracks -- were found projecting into the corpus callosum (Plate VI, figure at bottom).

- Farther off of the cerebral ventricles, the relative reluctancy of plaques to transgress the borders to the cortical grey matter is of particular interest: Rather than being conditioned by a local concentration gradient of some myelin constituent(s), the tendency of lesions to flatten out before impinging upon the relatively stronger pulsating cerebral cortex might testify to the greater effectivity of cortical arterial counterimpacts.

... The retrograde expansions of plaque veins -- and thus also of cerebral plaques -- must thereby be limited by pressure rises inside the involved vein, as well as inside the craniovertebral space as a whole, which suffice to cancel the thrust of the regurgitant blood. This explanation of lesion development admits solely of a very short timespan of brain plaque evolution, and it makes understandable why, as numerous pathologists -- from Dawson to Lumsden -- have noted again and again, brain lesions appear punched out "all in one piece".

Widening of cerebral veins is a strong, localized, counteracting influence and lesion spread is further limited at the cortical boundaries. There are some additional factors worth considering as well. Obliteration of brain tissue and vasculature will anatomically and rather directly limit refluxing blood volumes. The brain in MS patients atrophies at a rate of .7-1.0% per year (Ref). A patient could see a substantial reduction in brain volume with a commensurate decline in blood volume prior to reaching the SP diagnosis or a chronic disease state. Given that the focal lesion mechanic is heavily reliant on sufficient refluxing blood volumes for a sustained countercurrent, upstream spread, even small reductions in blood volume could abruptly curtail the process. Hemodynamic changes such as prolonged cerebral circulation time (CCT) and mean transit time (MTT) can functionally limit venous filling during a sustained bruxing episode. Prolonged CCT, MTT, and other hemodynamic abnormalities in MS will be explored in more detail later.
The pattern of T2 vs. T1 behavior of perivenous lesions illustrates the exhaustion of the lesion-generating mechanism. Ge writes (Ref),

Although MS lesion plaques can be found throughout the brain, they have a predilection for periventricular white matter and tend to have an ovoid configuration with the major axes perpendicular to the ventricular surface. At the initial stage, the lesions are typically thin and appear to be linear (Dawson’s fingers), which is probably associated with the inflammatory changes around the long axis of the medullary vein that create the dilated perivenular space (Fig 1). Histopathologically, such perivascular inflammation has been thought to play a primary role in the disruption of the blood-brain barrier (BBB), in myelin breakdown, and in the formation of new lesions. In addition to the periventricular region, the corpus callosum, subcortical region, brain stem, U-fibers, optic nerves, and visual pathway are also regions where lesions are frequently located. The focal demyelinating lesions located along the lateral borders of the corpus callosum are best depicted by sagittal fluid-attenuated inversion recovery (FLAIR) imaging (Figs 2 and 3). The abnormalities of the corpus callosum, U-fibers, and optic nerves, however, may allow for the differentiation of MS from cerebrovascular disease.

On T1-weighted imaging (T1WI), the acute MS lesions are often isointense to the normal white matter but can be hypointense if chronic tissue injury or severe inflammatory edema occurs. The accumulation of hypointense lesions (so-called black holes) may correlate with disease progression and disability. In the acute inflammatory phase, the lesion may disrupt the BBB, leading to gadolinium enhancement (Fig 2) that is believed to be the first detectable event on conventional MR imaging, and may last from days to weeks. Enhancing lesions, which may vary in shape and size; usually start as homogeneous enhancing nodules and subsequently progress to ringlike enhancements. Contrast-enhanced T1WI is now routinely used in the study of MS and provides one in vivo measure of inflammatory activity. It is able to detect disease activity 5–10 times more frequently than the clinical evaluation of relapses, which suggests that most of the enhancing lesions are clinically silent. In the chronic stage, lesions often appear as isointense or hypointense on T1WI and usually persist for many years on T2WI. Some patients may experience the expansion of a pre-existing lesion with or without enhancement.

The initial perivascular inflammation is the earliest detectable change on conventional MRI which is expected. Prior to this, there was either no reflux into the venous channel or it was not sufficiently damaging for macroscopic imaging to detect. Once the reflux becomes sufficiently injurious to the perivascular region, there is a breakdown of the BBB and increased permeability. During this period, a predilection for fluid filtration into these spaces may lead to vasogenic edema (Ref). As the perivascular tissue atrophies over time, the mechanical impacts and stretching reach a limit and the lesions will appear as hypointense black holes on T1 MRI. The black holes are enlarged VR spaces filled with CSF following atrophy.

A significant problem for many SPMS patients is worsening motor function as compared to the RRMS
stage. SPMS and PPMS patients demonstrate similar diffuse cervical cord damage which can account for some of the accumulating motor disability experienced by these patients. These changes are poorly detected by conventional MRI imaging techniques (Ref). The origin of the damage is poorly understood even though it has high correlation to functional disability (Ref). Gliotic changes and axonal degeneration have been found which eventually results in widespread atrophy (Ref). fMRI shows increased cord recruitment in SPMS vs. PPMS patients (Ref).

Wallerian degeneration from accumulating axonal loss in the brain probably accounts for much of the cervical atrophy and worsening motor function (Ref). Evangelou et al report,

> Atrophy is not the same in all parts of the cord. It has been recognized previously that different parts of the CNS show different degrees of atrophy (Edwards et al., 1999), but to our knowledge no study has compared atrophy in different regions of the spinal cord. We found atrophy in multiple sclerosis to be more prominent in the upper part compared with the lower part of the cord. This was not due to measurement error, as the cord becomes smaller below the cervical expansion. The cross-sectional area of the cord is significantly larger in the lumbar cord compared with the upper thoracic section (Mann–Whitney, P = 0.01), but still showed no evidence of atrophy as opposed to the upper thoracic cord. It might simply be that the lower parts of the cord have less white matter than the upper, which would suggest that cord atrophy is mainly a function of the white matter volume loss, despite evidence that, at least in the brain, grey matter volume loss is substantial (De Stefano et al., 2003; Sailer et al., 2003). The white matter atrophy could of course be either due to Wallerian degeneration, loss of myelin or to a combination of these mechanisms. The cervical cord is also affected by a higher lesion load than other parts of the cord, but overall we have found that lesions do not play a major role in local atrophy.

A correlation between spinal cord atrophy and white matter atrophy in the brain makes sense. Axonal loss is more pronounced in SPMS and PPMS than RRMS which explains the timing of marked cervical atrophy in the progressive forms. However, since white and gray matter atrophy commence from the outset of all MS types, cord atrophy would likewise commence from the outset even in early RRMS.
Clinical results of immunosuppressive and immunomodulatory treatment for RRMS and SPMS reflect such a disease evolution. The inflammatory response to a newly formed focal lesion can directly contribute to neurological deficits. Treating RRMS patients with steroids following an acute relapse can abate or resolve symptoms by suppressing the inflammation (Ref). “Disease modifying” drugs merely decrease the number of relapses by frontloading anti-inflammatory agents which mask inflammation from focal damage. The treatment regimen does not address the root causes of the disease which explains why they have little effect in the long-run. MS drugs are also ineffective in the progressive forms which feature a different inflammatory profile that mostly lacks the focal inflammation. The same study found that existing lesions re-enhanced within a few days of stopping treatment and that new lesions frequently formed within one month of stopping steroid treatment.

Secondary progressive MS patients exhibit more Type II and Type III MRI findings of the spinal cord which feature diffuse cord abnormalities.

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Explaining PPMS

Phantom-like Disease Mechanics

PPMS is a more chronic condition and typically surfaces after the age of 40, compared to an average age of 30 for RRMS. PPMS has more spinal cord involvement than then RRMS/SPMS pattern and smaller focal lesion loads. PPMS is also distinguished by far more severe motor impairment compared to the RRMS/SPMS pattern. A recurring question raised over the years is whether or not PPMS is a type of MS or a different disease altogether. Under the autoimmune paradigm, PPMS does indeed present an explanatory challenge much like SPMS. When MS is viewed through a biomechanical lens, a related but different biomechanical pathology can explain why we observe a related but in many ways different disease.

In PPMS, the cranial bone movement is more subtle which leads to a different pattern of disease. Skull morphology in combination with weakened sutures and other factors synergistically work together to render ephemeral, less displacive, but chronic cranial bone movements to become insidiously injurious. Jaw movements from routine behaviors such as chewing food, speaking, diurnal bruxing, yawning, and swallowing can eventually become injurious. Prior to diagnosis, the disease had likely been progressing for many years, silently accumulating axonal loss and changing the structural properties of the brain tissue and spinal cord. To be sure, the RRMS disease process can go undetected as well but owing to its more volatile nature and the highly symptomatic focal damage, it is more likely to flare up and get diagnosed in the twenties or teens, sometimes even in childhood. Consistent with a more chronic but less volatile disease mechanic is a more predictable clinical course, lack of focal lesions, atypical acute ON, and more symmetrical symptomatology.

Like in RRMS/SPMS, the squamosal suture in PPMS is probably overly-compliant but it is the particular morphology of the patient’s skull that allows routine jaw movements through the TMJ to sufficiently shift the cranial bones. A hypothetical example of a predisposed skull could be a male Caucasoid skull with a mild form of frontosphenoidal craniosynostosis. Frontosphenoidal craniosynostosis exists on a spectrum, probably goes undiagnosed frequently, and can cause a “pinching” at the temples. The narrowing of the skull along the temporal parietal suture in the direction of the frontal bone could exaggerate the upward-rearward displacement of the parietal bones when the squamous portion of the temporal bone glides out. The bilateral temporal bone displacement could be within normal limits but the upward displacement of other cranial bones may not be. A malpositioned superior border of the temporal bone could be significantly involved in these types of cases. Williams et al report,

Indeed, temporal bone movement (mean angle of change at the suture) is about 1.75°. Other measurements indicate that this magnitude of movement is common in most sutures in most crania.5 Indeed our current, unpublished 3D radiographic imaging studies demonstrate the presence of a malpositioned superior border of the temporal bone in patients with MS. This observation led the authors to hypothesize that periodic episodes of bruxism may be associated
with increased intracranial pressure, which in turn, might be associated with demyelination in
patients with MS.

An effort must be made to identify predisposed patterns especially given racial, gender, and ordinary
variation in cranial morphology. While nocturnal jaw clenching in PPMS may not be as damaging as in
the RRMS pattern, these episodes can still be expected to be far more damaging than routine diurnal
jaw behaviors. In PRMS patients, the bilateral displacement is sufficient to replicate the RRMS focal
lesion-generating process as well as having additional factors enabling the disease to be chronic from
the outset. These patients usually have the most aggressive disease course and worst prognosis.

In order for subtle cranial bone movements to become injurious, co-existing factors that functionally
intensify these forces will likely be present. Examples include anatomical obstructions (congenital or
acquired) in the posterior cranial fossa (PCF), obstructions at the cranio cervical junction, hypoplastic
jugular foramina, spinal stenosis, vascular hypoplasia, or missing extracranial veins. Another possibility
that will be explored in more detail is a reduction of spinal compliance. Zamboni found a combination of
agenesia and atresia of the lumbar venous tree in PPMS patients, in addition to multilevel stenoses in
the azygos. The resulting hemodynamic pattern features shunting of blood up the vertebral venous
plexus which would directly impede venting from these veins from changes in CSF pressure. More
mundane factors that can also affect spinal compliance include obesity and routine situations of
increased intra-abdominal pressure. The compliance of the spinal thecal sac is essential for optimal
windkessel function and protection of the CNS from external mechanical forces.
Let’s return to Bergsneider and Egnor to better understand how this works at the conceptual level. In our original harmonically-tuned model consisting of a block suspended by a spring and another carefully selected weight and spring, let’s say that the spinal CSF compliance has been compromised which could be represented by a stiffer spring suspending the weight. The magnitude of the fluctuations of the block would increase because of the harmonic resonance mismatch. Let’s assume for now that vascular autoregulation is not present. We can represent an external ephemeral force from cranial bones on a closed box CSF system by a quick downward tug on the weight. Since the spring connecting the weight to the block is stiffer than normal, the block will experience an exaggerated longitudinal strain. The strain exerted on the block will largely depend on the force and timing of the tug, given that the block is experiencing bounding fluctuations. If the block is in the process of bounding upwards when the tug is made, then an increased stretching force will be exerted on the block. The earlier the tug is made when the block begins to bound upward, the greater the force exerted on the block. The stretching strain in this model is in practice the compressive (ICP) strain exerted on the brain parenchyma and capillaries by deflecting cranial bones. The force delivered to the brain tissue would depend to a good degree on the instantaneous state of the capillary system (stimulating the system at the fundamental harmonic frequency).

To make the model more realistic, let’s incorporate vascular autoregulation. To dampen fluctuations, the brain will finely constrict cerebral arterioles. This can be represented by a carefully chosen stiffer spring to suspend the block such that the magnitude of the block’s fluctuations diminish and become harmonically tuned with the weight and spring. Under this new homeostasis, an effective minimum or “baseline” stretching force is imposed on the block due to the inherent rigidity of the two springs in the system. The ICP change in this system will depend more on the deflective force and the inherent biophysics of the system and less on its instantaneous state. That is, a chronic and insufficiently-
compensated mechanical disease state is facilitated. Observe that this system and the original system are both harmonically tuned but respond differently to an external force. Obesity-associated IIH is an excellent and extreme example of compromised spinal compliance. It should be readily apparent why any physiological imbalance that leads to increased ICP will also lead to increased risk for developing MS.

The overall pattern of damage in PPMS is one characterized by more diffuse damage to cerebral axons throughout the disease course. Since venous filling is less pronounced in PPMS, there is a smaller but more distributed overall lesion load. Ingle et al write (Ref),

Quantitative T2 lesion and T1 hypointensity load data (calculated with computer-assisted visual or semi-automated algorithms) have been presented in several studies. These studies confirm that PPMS tends to have lower lesion loads (Tables 2 and 3) (4-9). Two earlier studies that used a scoring system based on lesion size are not included (10,11). In these studies, T2 load was greater in SPMS than PPMS with ratios of 1.0:1.6 and 1.0:2.2 (PPMS:SPMS). The study of Filippi et al. found that the areas where difference in lesion load was greatest between patients with PPMS and patients with SPMS were the frontal, occipital horn, and trigone areas and the parietal and temporal lobes (11).

In addition to finding lower lesion loads in PPMS compared to SPMS, Lycklama á Nijeholt et al. reported a lower ratio of T1 hypointensity to T2 load in PPMS (14). This was seen too, although to a less marked extent, in the study of van Walderveen et al. (8). Patients with PPMS in this
study were found to have a higher incidence of diffuse hyperintense brain abnormalities on proton-density-weighted images when compared to patients with SPMS (9 of 31 patients against 3 of 28 patients). These diffuse abnormalities were found mostly in the parietal periventricular white matter.

Due to the inherent biophysics in PPMS, subtle pressure gradients are transmitted from the cranial subarachnoid space to the ISF, cerebral capillaries and brain tissue, and to various CSF cisterns. The force exerted on the brain in this hypothetical patient would be greatest at the sides of the brain and in the CSF spaces sensitive to up and down forces acting on the CNS. PPMS patients typically show significant atrophy of the bilateral central sulci (precentral and postcentral gyri), bilateral middle temporal gyri, and the prepontine and quadrigeminal cisterns (Ref). For comparison purposes, an upwards central transtentorial herniation is radiographically characterized by obliteration of the quadrigeminal cistern while downward transtentorial herniations typically cause prepontine cistern widening.

Extensive atrophy of the precentral and postcentral gyri can also be accounted for by retrograde axonal degeneration from accumulating mechanical damage to the pyramidal tracts on the flanks of the spinal cord. Investigations into atrophy, disability, and cortical reorganization following trauma to the spinal cord acknowledge the role of retrograde degeneration (Ref). Freund et al write,

> Overall, the reduction of subcortical white matter volume in the corticospinal tract and cortical grey matter volume and cortical thinning in primary motor cortex is indicative of atrophy due to retrograde degeneration (Hains et al., 2003; Beaud et al., 2008), but could also arise from
decreased cortical connectivity due to a reduction in dendritic spine density (Kim et al., 2006) or a reduction in angiogenesis (Fields, 2008). Atrophy of neurons in primary sensory cortex may be induced through reduced cellular activity, triggered by transneuronal degeneration (Jones, 2000). CNS atrophy and its relationship with clinical impairment may prove to be a pathologically specific marker in clinical trials of spinal cord repair, as brain volume change has been used as an outcome measure in trials in patients with multiple sclerosis (Barkhof et al., 2010).

Depending on the nature of the injurious forces in a PPMS case, the brain MRI could theoretically appear quite normal save for very subtle changes to the normal-appearing white matter (NAWM) or microvasculature. Unlike the RRMS/SPMS pattern, the mechanical forces acting on the brain in PPMS are more subtle, diffuse, and evenly distributed leading to more generalized diffuse axonal injury as compared to RRMS/SPMS. These and other MRI findings lead Palace to remark quite accurately (Ref), MRI of the brain is often less abnormal in primary progressive MS, possibly as a result of more spinal cord pathology and/or a different pathological spectrum (that is, a more generalised axonopathy).

What can account for more extensive spinal cord involvement in PPMS, beyond Wallerian degeneration from cerebral atrophy?

Co-Existence of Injurious Spinal Cord Displacements

Atresia of the ascending lumbar venous tree can predispose one to more than just sustained or episodic (but fairly uncompromising) reductions of spinal compliance. Another insidiously injurious mechanic can manifest involving intermittent displacements of the entire spinal cord caused by vehement headward fluid displacements from the lumbar cistern. Again, a review of the regional venous anatomy will shed light on how such a disease mechanic is possible. The left and right ascending lumbar veins emerge from their respective common iliac veins. The right azygos vein terminates at the confluence with the right subcostal vein around L1 to form the azygos vein. The left ascending lumbar vein becomes the hemiazygos vein. The Lumbar cistern begins at L2 and terminates at S2. There are several immediate considerations of missing or hypoplastic ascending lumbar veins and similar abnormalities in the region:

1. During periods of sustained increased abdominal pressure, an overly large volume of blood will be shunted towards the epidural veins encompassing the lowermost portions of the thecal sac. Increased pressure on the abdominal wall has been shown to increase blood volume in the epidural veins (Ref). In cases where there is a congenital absence of the inferior vena cava, the ascending lumbar veins compensate and are enlarged. Therefore, if one or both of the ascending lumbar veins is missing, and if intraabdominal pressure conditions functionally prevent adequate blood flow through the inferior vena cava, then significant overburdening of the lumbosacral epidural veins is likely to occur.

2. If the left ascending lumbar vein is missing, the azygos vein and right ascending lumbar veins will likely be serving compensatory roles. Sudden increases in abdominal pressure may displace
large amounts of blood in the azygos vein in a cephalad direction. If met with membranous obstructions, an incompetent valve in the arch of the azygos, or other obstructions, blood will be shunted toward epidural veins and forcibly drained in an upward direction.

3. Since the ascending lumbar veins drain portions of the posterior abdominal wall, intrabdominal veins will serve a compensatory role thereby creating a tendency for overburdening and venous stasis within the abdominal compartment. These veins must drain either into the inferior vena cava or anastomose with veins of the lowermost dural sac. A number of events can cause a sudden displacement of this volume of blood into the veins encompassing the lowermost portions of the thecal sac.

4. Absence of veins draining the pelvic floor will shift the abdominal hydrostatic indifference point (HIP) cranially (Ref). The location of the HIP is determined by compliance, volume, and size of the intraabdominal compartment. Congenital venous malformations reducing compliance near the pelvic floor may create general conditions for reflux into lumbosacral epidural veins. The liver has a specific compliance of 25 ml kg\(^{-1}\) mm Hg\(^{-1}\), making it the most compliant of abdominal organs. It contains about 15% of the total blood volume and electrical stimulation of the splanchnic nerves has been shown to dispel up to 50% of liver blood volume. Therefore, the liver and hepatic venous system may serve as a pressure relief valve preventing venous reflux into lumbosacral epidural veins during routine functional changes in intra-abdominal pressure.

5. Any physiological influence that can increase intra-abdominal pressure could have an impact on the disease process, perhaps even worsening symptoms acutely for the duration of the increased abdominal pressure. Some examples include sudden flexure of abdominal muscles which could compress these veins such as a cough, sneeze, breathing, or an external mechanical impact. Urinary bladder pressure is a good indicator of intra-abdominal pressure and a full bladder could acutely exacerbate symptoms. Inflammatory conditions of the gastrointestinal tract, whether caused by the disease or something unrelated can also increase intra-abdominal pressure. A full stomach will affect the biophysics just by added volume and an empty stomach will induce powerful rhythmic abdominal muscle contractions that are part of the migrating motor complex. These contractions could easily shift blood in the lower abdominal regions or alter the compliance of the thecal sac for the duration of the hunger.
With the above considerations, let’s hypothesize a simple scenario that could cause reflux into lumbosacral epidural veins. Let’s say that the patient has been seated, leaning back in his chair for 15 minutes. Blood has a tendency to pool in the lower abdominal regions while seated. The patient suddenly shifts his body so that he is now slightly leaning forward. Such a shift in body weight to the abdominal region and concomitant abdominal muscle flexure could shift a large quantity of blood towards the lowermost epidural veins. Upon this occurring, the patient may acutely experiencing flashing lights, involuntary muscle fasciculations or contractions, neuropathic pain, and other symptoms consistent with the patient’s overall clinical decline.
Why did the patient experience those neurological symptoms upon making that movement? Longitudinal cord displacements will create tensile strains at the attachment points of the denticulate ligaments, eventually causing damage to the spinal cord. Schelling writes,

In comparing arterial as against venous conductivity, and the intensity of the pressure-dependent blood-displacements in the arteries as against the veins, the volume-displacements within the craniovertebral space, which are effected by local veins, can be expected to be far more effective than those of arterial vessels. This conclusion is corroborated by the results of studies on arterial and venous cerebrospinal fluid displacements, which show that far the most intense (endogenous) cerebrospinal fluid shifts are due to venous back-jets rushing back from veins inside the abdomen into veins encompassing the lowest part of the spinal dural sac (cf. Plate XIV, figg. C, D) (39, 111). There are individuals who have shown subarachnoid fluid shifts so vehement as to be likened to "plunger strokes" (136). Continually subjecting the spinal cord, in short-term repetitions, to this intrinsically self-aggravating mechanism, venous back-jet induced subarachnoid fluid displacements from the lower spinal canal may gradually become so intensified as to eventually be injurious. Dragging the spinal cord headwards, such intense subarachnoid fluid shifts may be capable of injuring the spinal cord by means of abrupt tensile impacts exerting their effects specifically along those fibrous structures which represent the spinal cord’s most stressed anchorages to the dural sac.
The outcome of these chronic strains is creeping fibrosis of the spinal cord’s flanks, damaging delicate neural tissue as it spreads. Fibrous tissue will undergo additional collagen formation when subjected to intermittent tensile loads by what is known as the stretch hypertrophy rule. From “Upper Cervical Subluxation Complex”,

Breig has shown that in flexion with elongation of the canal the distance between the dentate attachments to the dura increases and an axial pull is exerted which gives rise to transverse tension in the lateral banks of ligaments. The ligaments have then been placed in a position of tension giving strength and rigidity to these structures. These ligaments consist of collagen arranged in parallel bundles. Collagen supplies strength and rigidity in tension and in tension alone. Normally, all adjacent structures share in the distribution of the tensile forces unless certain individual ligaments are placed under a greater degree of tension, causing a local increase in rigidity. Fibrous tissue also follows what has been called the stretch hypertrophy rule. Living fibrous tissue structures when exposed to a series of intermittent elongating tension loads undergo additional formation of collagen. Although such alterations occur only with intermittent tension loads, it appears reasonable to assume that the dentate ligaments in certain instances of cervical spondylosis undergo stretch hypertrophy, resulting from tension occurring intermittently when the cord is in ventro-flexion.
Newley called it tenseness was shown in 30% of cases. "The Reproductive Syndrome" by Paul Chek, 1995; A figure shows a diagram of the spinal cord and nerve tracts induced by upper cervical subluxation via dentate ligaments. Laminar arrangement of spinal tracts is also shown.
Oppenheimer confirmed the relationship of the fibrous flank lesions and their relationship to the denticulate ligaments, and favored a mechanical explanation for their origin (Ref). He attributed many of flank lesions to vascular hemorrhages caused by tension from the denticulate ligaments. As the ligaments undergo additional collagen formation and become more rigid, they lose their ability to dissipate energy from further tensile forces. Instead, the energy is transmitted to the pia mater of the spinal cord where the denticulate ligaments attach. The pia mater is richly endowed with blood vessels that are constricted by undue mechanical strain leading to microvascular hemorrhage. Oppenheimer also cautioned against neck flexion in patients where Lhermitte’s sign was present, due to mechanical tension on the cervical spinal cord that could lead to microvascular hemorrhage (Ref). Extensive pyramidal spinal cord damage of this nature will cause retrograde axonal degeneration in the brain, particularly of the precentral gyri.

Poser has documented that spinal cord lesions in MS tend to have an anatomical correspondence to cervical spondylosis (Ref). Oppenheimer also noted the invariability of lesions at the C7 level. The C6-C7 level is the “junction point” when the neck moves from flexion to extension and C5-C7 is the most common location for cervical spondylosis (Ref, Ref). It could be hypothesized that, since these ligaments are already placed under increased tension due to normal cervical kinematics, their ability to dissipate intermittent axial tensile strains could be diminished. Thus, there could be a predilection for lesion formation in these regions.

The gradualness of such a mechanical process becoming injurious must be emphasized and would progress at varying rates. Anatomical predispositions and environmental influences would significantly impact the progression of such a mechanism. Gradual washing out of involved veins would self-aggravate the process. Schelling writes,
Again, to cause the continual venous regurgitations into the lower spinal canal to individually attain injurious intensities, a mere progressive washing out, i.e. widening, of their own pathways and of those for the simultaneous venting effluxes may be sufficient. The strength of the individual retrograde flows will thereby tend to increase in proportion to the speed and ultimate height of the ascent of any infradiaphragmal, i.e. intraabdominal excess pressure -- dependent on the preceding emptying of the veins of the lower spinal canal. This emptying predisposes to more massive regurgitations, both directly and by a relatively stronger filling of separate veins providing the compensatory venting of the craniocervical space. Spinal regurgitation, however, differs from cerebral as to the far greater number and complexity of the venous pathways connecting the intraabdominal collecting veins to the venous plexuses encompassing the lowermost part of the spinal dural sac.

Bodily kinematic changes stemming from disease progression also need to be emphasized given the motor impairment of PPMS. Weakening of core muscles in the back will shift responsibility to other muscle groups proximal to larger and more readily-displaceable venous blood volumes, especially those of the abdomen and abdominal wall. Thus, routine bodily movements may induce more frequent and forceful abdominal muscle flexure, weight-bearing, and sudden changes to intra-abdominal pressure leading to more chronic venous reflux into epidural veins and worsening disease progression.

**Venous Reflux into Isolated Vertebreal Levels**

Zamboni observed an anatomical correspondence between typical flank lesions of the spinal cord and collateralized blood flow perpendicularly shunted towards epidural veins due to multilevel obstructions of the azygos vein. If the blood is shunted under sufficient pressure and velocity, this could displace the CSF fluid and spinal cord posteriorly and rather focally. Schelling writes,

> The spinal cord can be selectively injured in its sides either by being displaced posteriorly, relatively to unyielding lateral fixations, by a blunt impact upon its front (57), or also - in virtually any location - by an interference of particularly rigid outer spinal cord fixation(s) with the cord's up or down movements relative to the dural sac (73, 142). Violent impacts upon an individual's back effectuating sharp intradural displacements and, in particular, vehement subarachnoid fluid shifts, have been observed to actually lead to widely scattered, anchorage-related damages to the spinal cord's flanks (12, 88, 122).
In cases where there is an isolated focal spinal cord lesion without any other obvious longitudinal cord involvement, and effort should be made to determine if abnormal hemodynamics can account for the lesion. Flank lesions are mechanically and not ischemically caused, although ischemia can secondarily occur. Even mildly abnormal venous flow patterns under normal conditions, especially in the azygos, can be exacerbated intermittently during routine daily activities. In this regard, studies of venous hemodynamics are sorely lacking in comparison to arterial studies, leaving us with a rather poor understanding of venous-related pathologies.

Such a mechanic could easily be present in the RRMS/SPMS pattern, as well as the spinal cord displacement mechanic. Likewise, ephemeral cranial bone movements can be injurious in RRMS cases as well. All of these overlapping injurious mechanisms reflect the inadequacy of the clinical phenotypes and why a total redefinition of MS is inevitable.

**Mountains of Evidence**

*MS is a Global Brain Disease*

For a long time the focal lesions that gave MS its name received most of the attention. However, more recent evidence is revealing diffuse global damage present throughout the white and grey matter from onset. The diffuse damage accounts for most of the accumulating disability and the visible T-2 lesion load correlates poorly with clinical disability. PPMS patients typically show subtle abnormalities on brain MRI despite usually severe disability while RRMS patients may show dozens of lesions yet minimal to no disability. With the increasing recognition of MS as a global disease, authors have begun to try to
understand the relationship between these two types of damage. Stefano et al. concluded (Ref),

Cerebral NAA/Cr and MTr values are diffusely decreased in MS patients with early disease, low demyelinating lesion load, and no significant disability. This suggests that axonal and/or tissue injury begins very early in the course of MS and might be at least partially independent of cerebral demyelination.

Lassmann et al. observed the predominance of focal lesions in RRMS and greater diffuse damage in the NAWM and cortex of SPMS and PPMS patients and concluded that there was only marginal correlation between focal lesion load and diffuse white matter or cortical pathology (Ref).

While researchers caught up in the autoimmune paradigm are scrambling to make sense of the diffuse global brain damage and focal brain lesions, our postulated mechanism of injury involving cranial expansions and contractions powered by the jaw muscles provides a remarkably natural explanation for these two patterns of damage in MS. At the moment cranial contractions become injurious, virtually the entire brain will be afflicted whether or not focal lesions are present. This explains what numerous other researchers have observed, that there is diffuse global brain damage from the outset of the disease. This enables the disease to progress subclinically for some time before symptoms manifest and a diagnosis is made. In the RRMS/SPMS pattern, this usually involves what’s called a relapse and focal brain lesions will be present. In the case of PPMS, this may only involve subtle motor impairment or other symptoms, sufficient to be noticed by the patient and brought to the attention of a doctor, but possibly without the presence of focal brain lesions.

It stands to reason that conventional imaging is unable to detect much of the diffuse damage because it
is occurring on a microscopic level. Lesser used radiological testing techniques such as MR elastography (MRE), MR spectroscopy (MRS), perfusion MRI, and diffusion tensor (DT)-MRI are revealing multiple pathological changes in MS of a global nature. Some of these include viscoelastic degradation of the brain tissue, DAI, and widespread ischemia. Even with these improved testing techniques, the dynamic nature of the disease process calls for more real-time in vivo imaging. The biomechanical hypothesis for MS provides a comprehensive explanation for these lesser detected but clinically significant pathological changes.

Diffuse Axonal Injury

DAI is typically the outcome whenever an acceleration/deceleration or rotational force is applied to the brain, causing tissue to slide over other tissue resulting in a shearing injury. Like in other instances where an external force is applied to the brain, the brain in this model will exhibit separate compressive (ICP) and shearing responses. As a general rule, cerebral degradation in MS will mainly be a function of the frequency and intensity of these compressive and shearing strains. If the cranial expansion-contraction is lopsided due to a functional jaw imbalance or marked cranial asymmetry, then a stronger shearing strain may be exerted on the brain tissue which is more damaging than a compressive strain. Cranial asymmetry can be influence by congenital and environmental factors as well as a left-right jaw imbalance. Recalling Behan and Chaudhuri's criticism of the autoimmune model and the association between MS and neurofibromatosis-1, neurofibromatosis-1 can cause progressive cranial dysplasia and marked cranial asymmetry involving the squamosal/temporal bone, sphenoid bone, and the frontal bone (Ref). In this way, neurofibromatosis-1 can have a significant, causal relationship to MS by introducing abnormal craniofacial biomechanics.

MS patients have lower baseline NAA/Cr ratios (Ref). A lower NAA can be caused by reduced axonal volume either from axonal thinning or a fewer number (Ref). More evidence of degradation of the tissue matrix comes from Stefano et al. who found decreased MTr in the normal appearing white matter (NAWM) of early RRMS patients with low lesion load and no disability (Ref). The authors write,

In addition to decreases of NAA/Cr, we also found decreases of MTr in the NAWM in this group of nondisabled MS patients. Magnetization transfer imaging of the brain is based on the interactions between the free water protons and protons attached to macromolecules, and a low MTr indirectly reflects tissue (matrix) damage.47,48 Several studies have demonstrated marked MTr reductions in lesions and NAWM of patients with MS.49,50 As recent studies have shown that focal MTr decreases in NAWM can occur before lesion appearance on conventional MR imaging,51-53 a low MTr in the NAWM may reflect subtle, microscopic, or molecular pathology of myelin in macroscopically normal white matter. Edema, astrocytic proliferation, perivascular inflammation, and demyelination may all contribute to a decreased amount of water bound to macromolecules in the NAWM and, as a consequence, reduced MTr.47 These pathologic features, however, are not prominent in the NAWM in early MS. A potential mechanism for subtle molecular alteration of myelin remains to be determined, but its presence is suggested by the fact that MTr values are decreased in the white matter of patients with MS who have completely normal results of conventional MR imaging of their brain.23 In addition,
since MTr decreases in postmortem brain of MS patients also correlate with axonal loss, it may be possible that membrane alterations associated with axonal injury also contribute to the decreases in Mtr.

These findings are in line with Traboulsee et al. who found that disability correlated with MTr abnormalities in the normal appearing brain tissue (Ref). Axonal loss is the primary disease metric of MS and those tests that measure for it will more accurately reflect disease burden. Axons play a crucial role in maintaining the structural and viscoelastic integrity of the brain, and their destruction commences a cascade of secondary consequences.

**Viscoelastic Degradation of Brain Tissue**

The sensitivity of MRE to microscopic structural changes in tissue allows quantification of some of the occult damage in MS. In MRE of the brain, harmonic vibrations are used to induce shear waves within the skull which are then used to compute the viscoelastic constants of the brain tissue. The viscoelastic constants are determined by the mechanical properties and interactions of neurons, glial cells, and the vascular tree. These viscoelastic parameters are heavily influenced by vascular, ISF and CSF pressure waves (Ref). The cardiovascular and respiratory systems constitute the major source of these waves under normal conditions. Recent evidence shows degradation of the brain’s mechanical integrity and accelerated loss of stiffness in MS (Ref). Viscoelastic alteration of the brain has long been an underappreciated factor in proper windkessel function and onset of chronic disease states such as hydrocephalus. Henry-Fuegas explains (Ref),
Thus, although disturbances in intracranial pulsations play a key role in the new hydrodynamic concept of chronic hydrocephalus, it can be noticed that hydrocephalus is not systematically associated with conditions that induce an isolated increase in arterial pulsatility (such as aortic insufficiency, hypercapnia) or a reduction in CSF venting from the cranial cavity – such as spinal stenosis [110]. Indeed, onset of chronic hydrocephalus appears to be modulated by the elastic properties of the brain [111] and it rather requires at least moderate failure of all the components of the multifactorial and sophisticated windkessel system.

In early RRMS, the viscoelastic changes indicate weakening and loss of structural integrity of the mechanical network of the parenchyma while the topology of the network remains relatively intact (Ref). After conversion to SPMS or if the disease was PPMS from outset, the weakening is accelerated but the topology undergoes significant deformation as well (Ref). Kaspar et al. found that the shear elasticity parameter $\mu$ was reduced by 12.7% in RRMS patients while changes in the powerlaw exponent $\alpha$ were uncorrelated. In chronic progressive MS, $\mu$ was reduced by 20.5% while $\alpha$ was reduced by 6.07%. Citing Kamphues et al., these findings led the authors to hypothesize,

The principal relationship between powerlaw exponent $\alpha$ and the hierarchical architecture of biomechanical networks was illustrated in [16] by numerical simulations and multifrequency MRE experiments of skeletal muscle. It was stated there that an increase in the fractal dimension of the network (given in contracting muscle by the establishment of myosin cross bridges) yields to an increase of the powerlaw exponent $\alpha$ while $\mu$ is influenced by the network-inherent spring constants quantifying the mechanical integrity of the underlying tissue.

Translating these findings to brain viscoelasticity in MS leads us to the following hypothesis: In early disease stages the integrity of the mechanical matrix is degraded while its inherent
geometrical order is preserved. However, this order becomes affected during further disease progression, resulting in a continuous decrease of $\mu$, but furthermore also to a reduction in $\alpha$.

The latter process may occur either in a slow and continuous manner, or by discontinuous remodelling of the tissue similar to a phase transition from an ordered to a disordered state of the brain parenchyma. To date it is not entirely clear which kind of mechanical cerebral tissue structure determines $\mu$ or $\alpha$. Recent in vivo MRE experiments in mouse models suggested that both demyelination and inflammation contribute to the observed deterioration of the cerebral mechanical scaffold [27], [28].

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<tr>
<td>female N</td>
<td>9 (sp)/4 (pp)</td>
<td>22</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>age</td>
<td>32 (19.51)/1 (3.3)</td>
<td>48 (9.7)</td>
<td>38 (8.0)</td>
<td>37 (11.4)</td>
</tr>
<tr>
<td>mean EDSS</td>
<td>5.6 (1.3)/5.3 (1.8)</td>
<td>0</td>
<td>1.6 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>$\mu$ in kPa</td>
<td>1.513 (0.176)</td>
<td>1.636 (0.008)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>$\Delta\mu$</td>
<td>–0.123</td>
<td>–7.52%</td>
<td>R = –0.4462</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>$\mu$ (in kPa)</td>
<td>2.607 (0.462)</td>
<td>2.372 (0.314)</td>
<td>3.025 (0.459)</td>
<td>3.545 (0.556)</td>
</tr>
<tr>
<td>$\delta\mu$</td>
<td>–0.67</td>
<td>–0.52</td>
<td>R = 0.0515</td>
<td>R = 0.4604</td>
</tr>
<tr>
<td>$\Delta\mu$</td>
<td>–20.46%</td>
<td>–14.66%</td>
<td>R = 0.001</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.2736 (0.0168)</td>
<td>0.2934 (0.0086)</td>
<td>0.2931 (0.0129)</td>
<td>0.2928 (0.0131)</td>
</tr>
<tr>
<td>$\Delta\alpha$</td>
<td>–0.0178</td>
<td>0.0009</td>
<td>R = –0.6786</td>
<td>R = 0.0333</td>
</tr>
<tr>
<td>$\Delta\alpha$</td>
<td>–6.07%</td>
<td>0.29%</td>
<td>R &lt; 0.001</td>
<td>P = 0.770</td>
</tr>
</tbody>
</table>

In a biomechanical study of the brainstem, Margulies et al. have shown that the structural strength of the brainstem is mainly derived from the axons rather than the surrounding matrix of astrocytes and oligodendrocytes [Ref]. Again, RRMS has a more localized distribution of pressure gradients with less extensive global axonal involvement until later stages. Once axonal loss becomes more widespread (i.e. degradation of the mechanical matrix) then the underlying geometrical order becomes more exposed and increasingly disorganized.
Hemodynamic Dysfunction

Imagine a brain that is softer than normal. Other things being equal, the tight expansion, contraction, and rhythmic displacement of the brain necessary for proper windkessel function would no longer be possible. The brain tissue would mechanically behave more sluggishly or “glob-like” and the diastolic compression necessary to squeeze out venous blood would be weaker and delayed. Since the venous system is more functionally dependent on the mechanical properties of the brain, the peak of the venous curve is shifted to the right and dampened, thus the arteriovenous delay (AVD) is elongated. Increasing venous resistance from worsening endothelial dysfunction and endovascular inflammation contributes to further elongation and dampening of the venous curve. If venous flow is delayed, other things being equal, the arterial bolus must also be delayed to prevent damaging spikes in ICP. Prolonged MTT and CCT are significant clinical findings in MS (Ref, Ref, Ref, Ref, Ref). Paling et al write,

Previous studies have demonstrated alteration in overall cerebral hemodynamics in MS. Cerebral circulation time, the difference in the arrival time of ultrasound contrast agent between the carotid artery and cerebral vein, was shown to be significantly prolonged in patients with MS (6.47 versus 5.54 seconds, P<0.001).14 Other studies using MRI contrast methods have shown significant prolongation of mean transit time, a measure of the average time contrast takes to transit from the arterial to venous circulation.15, 16, 17 These studies have indicated that prolongation of cerebral hemodynamics occurs in MS, but were not able to ascertain whether prolonged times were due to arterial or venous factors, as the methods were not able separate their effects. This study extends these observations by demonstrating that the cerebral arterial hemodynamic measure BAT is significantly prolonged in NAWM and deep gray
matter in MS, independent of age, gender, and brain atrophy. We also found significant associations between EDSS and BAT in NAWM and deep gray matter, independent of age, gender, BPF, and T2 lesion load. These findings and possible pathophysiological causes will be discussed in turn.

Since blood remains in the intracranial space for a prolonged period of time, hemoglobin concentrations may diminish and widespread hypoxia could occur (Ref, Ref, Ref, Ref). On MRI imagery dependent on oxygen saturation, these changes could contribute to a loss of visibility of the venous vasculature. Zivadinov et al write,

SWI is very sensitive in detecting signals from substances with magnetic susceptibilities that are different from that of their neighbors. Consequently, SWI is able to detect tissue iron in the form of ferritin, hemosiderin and deoxyhemoglobin, [25,33,34] and is sensitive to the visualization of small veins in the brain [10]. SWI venography allows detailed visualization of cerebral veins in the brain parenchyma without the use of an exogenous contrast agent [9]. This is possible by exploiting the difference in magnetic susceptibility properties between oxygenated and deoxygenated hemoglobin. The abundance of the paramagnetic deoxyhemoglobin molecule in the venous blood results in increased local magnetic field inhomogeneity, which in turn leads to spin dephasing and signal loss on SWI venography, resulting in decreased VVV [10].

As the disease progresses, there is an obliteration of the brain tissue and cerebral vasculature. Zivadov et al. concluded that reduced visibility of the venous vasculature is a combination of reduced metabolic demand and morphological changes to the venous vasculature necessitating a rerouting of blood flow.
Loss of smaller venous vessels will overburden some of the remaining larger vessels creating fairly localized delays within the venous system. Zivadinov et al write,

Contrast-enhanced SWI significantly increases the visualization of number and volume of signal hypointensities on SWI venography [28,29] in T2 lesions and in normal appearing WM (Figure 4), and may be an additional means of investigating whether SWI venography differences between MS patients and HC are due only to hypometabolic status or whether morphological changes of veins may be taking place in MS patients. 81.4% of the MS patients and 21.2% of HC included in this study underwent both pre- and post-contrast SWI sequence in order to further elucidate this important question. We demonstrated a very similar decrease in brain parenchyma VVV on pre- and post-contrast SWI parameters we examined in MS patients, but significantly increased ATVV and ATVV of veins with a diameter < .3 mm in HC was found, as expected (Table 4). The reduction of vascular visibility on pre-contrast SWI between MS patients and HC was previously observed and attributed to hypometabolic status in brain parenchyma of MS patients [10]. However, the pre- and post-contrast SWI venography experiment performed in the present study further extends understanding of this phenomenon and suggests that the reduced VVV in MS may be a combination of two main effects - reduced metabolism and morphological changes of the venous vasculature.

This loss of vasculature suggests that rerouting of the intracranial venous blood flow is probably taking place. If CCSVI is secondary to various vascular, infective and inflammatory processes (this hypothesis could explain the presence of CCSVI in HC), then the tendency to be chronic in its development may help explain the temporal dissociation between the loss of the VVV and no development of intracranial hypertension. In that context, hemodynamic compensatory mechanisms may play a key role. One such mechanism could relate to the development of extra-cranial collateral circulation [14,16] or altered CSF dynamics [17] that would compensate for altered primary outflow pathways.
Over time, atrophy of brain tissue and vasculature directly contributes to reduced CBF and CBV (Ref, Ref, Ref, Ref). Zivadinov et al write (Ref),

We found a reduction in CBF in deep gray matter in patients with MS; however, this was not independent of atrophy assessed by BPF. This suggests that reduction in CBF is secondary to reduced metabolic demand secondary to neuroaxonal loss.\(^3\) This would concur with a recent large study reporting an association between reduced cortical gray matter CBF and increased T2 lesion load. This study found that of all the variables tested, that white matter lesion load had the strongest association with cortical perfusion reduction,\(^3\) suggesting that focal lesions cause neuroaxonal disruption, which leads to a reduction in metabolic demand in the cortical gray matter, and hence reduction in perfusion.

7T MRI findings show widespread microvascular changes normally not detected by lower-field MRIs (Ref). Again, this is expected considering that cerebral blood vessels will globally experience transient spikes in pressure resulting in widespread ischemia (Ref). Chronic inflammation from episodic mechanical insults contributes to impaired tissue reperfusion, particularly of smaller occluded venous vessels. Endothelin-1 levels are significantly elevated in MS patients (Ref, Ref). Murray et al write (Ref),

Systemic interleukin-1 caused a severe reduction in cerebral blood flow and increase in infarct volume compared with vehicle. Restriction in cerebral blood flow was observed alongside activation of the cerebral vasculature and upregulation of the vasoconstricting peptide endothelin-1 in the ischemic penumbra. A microthrombotic profile was also observed in the vasculature of rats receiving interleukin-1. Blockade of endothelin-1 receptors reversed this
hypoperfusion, reduced tissue damage, and improved functional outcome.

... These data suggest patients with a raised inflammatory profile may have persistent deficits in perfusion after reopening of an occluded vessel.

Cerebral autoregulation is designed to handle routine changes in blood pressure such as during physical exertion. In a disease like MS where the system is subjected to chronic changes in ICP and mechanical changes to the brain tissue, cerebral autoregulation could be rendered systemically dysfunctional. Paulson et al write (Ref),

**Autoregulation of blood flow** denotes the intrinsic ability of an organ or a vascular bed to maintain a constant perfusion in the face of blood pressure changes. Alternatively, autoregulation can be defined in terms of vascular resistance changes or simply arteriolar caliber changes as blood pressure or perfusion pressure varies. While known in almost any vascular bed, autoregulation and its disturbance by disease has attracted particular attention in the cerebrovascular field. The basic mechanism of autoregulation of cerebral blood flow (CBF) is controversial. Most likely, the autoregulatory vessel caliber changes are mediated by an interplay between myogenic and metabolic mechanisms. Influence of perivascular nerves and most recently the vascular endothelium has also been the subject of intense investigation. CBF autoregulation typically operates between mean blood pressures of the order of 60 and 150 mm Hg. These limits are not entirely fixed but can be modulated by sympathetic nervous activity, the vascular renin-angiotensin system, and any factor (notably changes in arterial carbon dioxide...
tension) that decreases or increases CBF. Disease states of the brain may impair or abolish CBF autoregulation. Thus, autoregulation is lost in severe head injury or acute ischemic stroke, leaving surviving brain tissue unprotected against the potentially harmful effect of blood pressure changes.

With so many hemodynamic abnormalities, MS patients are bound to suffer symptoms stemming from poor CBF. Chronic fatigue is a major problem plaguing MS patients and likely has its roots in inadequate CBF.

Lastly, marked increases to CCT and MTT will impair the brain’s cooling mechanisms possibly leading to heat intolerance. The brain resides in an enclosed container with only a few outlets yet puts off large amounts of metabolic heat due to the enormous amount of energy it consumes. These two factors create the tendency for an overheating problem which requires an efficient cooling system to prevent brain damage. Flanagan explains the crucial role of veins in keeping the intracranial compartment cool (Ref).

The cranial veins of the face and scalp are on the outside of the skull where the cooling process begins with conduction, convection and sweat evaporation through the skin. The diploic veins, seen in the picture above, sit between the inner and outer plates of the membranous bones of the skull that cover the cranial vault. The emissary veins connect the veins of the face and scalp both to the diploic veins and the dural sinuses.

... The cooled venous blood from the face and scalp can thus flow through emissary veins and into the diploic veins between the inner and outer layers of bone that form the cap over the brain. It can also flow through the skull and into the dural sinuses inside the cranial vault. The emissary veins thus cool the dural sinuses directly (see picture above). They also keep a cooler layer of blood in diploe between the bones of the skull.

... Lastly, the most important feature of the brain cooling system is the heat exchanger mechanism used by humans. In this case venous blood that has been cooled by cranial veins of the face and scalp flows through dural sinuses that serve as counter-current heat exchangers that cool incoming arterial blood before it enters the brain.

If you look at the picture above of the main dural sinus of the drainage system of the brain, you will see the internal carotid artery, depicted in red, passing through the venous cavernous sinus (blue) before it enters the brain. Several veins from the face drain cooled blood into the cavernous sinus thus allowing it to act as a heat exchanger for arterial blood entering the brain. As an aside, it is interesting to note that the largest vein that plays a role in cooling the cavernous sinus is the ophthalmic vein, which drains the eye. The exposed surface of the eye thus helps cool the brain.
Since intracranial blood flow is exceedingly sluggish in MS, blood is exposed to metabolic heat for an overly long period of time. The temperature in the veins will tend to increase which in turn reduces the cooling of incoming arterial blood, thus reducing the overall cooling capacity of the system. Hemodynamic dysfunction is probably one of the two biggest contributors to heat intolerance in MS patients, the other being dysautonomia due to brainstem damage (Ref). Hyperthermia has numerous adverse effects on the brain, both under normal conditions and in disease states.
Vitamin D Deficiency and MS Risk

Vitamin D is essential for proper bone mineralization and density because it aids in the absorption of calcium. Ever since Goldberg first proposed a relationship between vitamin D deficiency and MS in 1974, the mounting evidence overwhelmingly shows that regions with low vitamin D levels have elevated rates of MS (Ref). MS incidence rises with increasing distance from the equator. Poser linked the Viking voyages to the current epidemiology of MS, which may explain why certain regions with heavy Nordic ancestry have high rates of MS such as Canada and Scotland (Ref). Many MS patients are found to be vitamin D deficient with poor bone health (Ref, Ref) and reduced bone density both at disease onset (Ref) and after many years of disease (Ref). Reduced bone density and mineralization along the cranial sutures is one of the essential causes of MS in this biomechanical model.
Recalling Behan and Chaudhuri's criticisms of the autoimmune model and its inability to explain the age effect of migration in MS, one study suggests that a vitamin D deficiency contributes to MS risk only if the deficiency occurs before the age of 15 (Ref). The data appears to suggest that the risk for developing MS later on in life can be “locked in” so-to-speak during the childhood and early teen years. The before 15 age-effect and gender gap in MS correlate tightly with typical gender differences regarding skeletal growth (Ref). Singh et al write,

The onset of puberty corresponds to a skeletal(biological) age of roughly 11 years in girls and 13 years in boys.19,20 The rates of increase in statural height and bone remodeling are greatest in early puberty followed by progressive decline.21 Consequently, peak vBMD velocity occurs 2 years later, at menarche in girls and late puberty in boys. The growth pattern in boys varies from girls in two ways: boys have two more years of prepubertal growth because of their later onset of puberty than girls, and pubertal growth spurt in boys lasts for 4 years compared to 3 years in girls.5,16,17 These differences widely account for the 10% greater statural height and the 25% greater PBM achieved by males.

By the age of 15, girls will have already hit their peak volumetric bone mineral density velocity and any environmental vitamin D deficiencies prior to this age could have a significant impact on MS disease risk well into adulthood, similar to osteoperosis. Since boys have a later and longer growth spurt and end up with overall greater bone mass, they have a lesser likelihood of developing MS. The skull can take up to 35 years to reach its peak bone mass so an environmental Vitamin D deficiency risk factor can strongly persist into the early thirties, close to the average age of onset of 30 for RRMS (Ref). These skeletal growth differences between men and women and the overall greater bone density in males accounts for
much of the male-female gap in MS incidence.

Genetic abnormalities involving bone density, craniofacial development, and suture health should be expected to be highly associated with MS. The CYP27B1 gene is one example and has also been associated with several other Vitamin D-related conditions. Individuals that carry mutations of this gene typically have lower levels of serum vitamin D (Ref). Ebers et el. searched over 3000 families of parents unaffected by MS that had a child with MS (Ref). In all instances the child inherited the mutated CYP27B1 copy, entailing odds of 32 billion to one. Another study also implicated the CYP27B1 gene in MS (Ref).
Taking a broader perspective, mutations of CYP27B1 have been known to cause pseudovitamin D-deficiency rickets (Ref). Rickets is a childhood disease caused by a vitamin D deficiency which can be of congenital or environmental origin. Frequent problems found in rickets include widened sutures, craniosynostosis and skull base defects. Abnormally large emissary foramina and abnormally small jugular foramina have been associated with craniosynostosis (Ref). Hypoplastic foramina have been associated with raised intracranial pressure and could significantly increase the risk of developing MS (Ref).
The biomechanical model of MS presented here readily satisfies Behan and Chaudhuri’s criticism regarding maternal contribution to MS disease risk. A longitudinal study found that decreased vitamin D during late pregnancy resulted in reduced bone-mineral content in offspring at 9 years of age (Ref). Similarly, maternal vitamin D deficiency can cause congenital rickets and the hereditary vitamin D-dependent type I rickets has been associated with MS (Ref, Ref). Additional maternal risk factors beyond bone mineralization and density can be passed along such as craniofacial developmental problems. An emerging and compelling hypothesis for the cause of autism involves inheritance of a cranio-mandibular disorder from the mother likely due to multigenerational vitamin D deficiencies. Jennings summarizes the working model (Ref),

1. the mother has a cranio-mandibular disorder that evidence shows is likely due to multigenerational dietary insufficiencies.
2. cranio-mandibular disorder causes a shift in neuropeptides with subsequent compromised neurodevelopment and epigenetic shifts.
3. mother gestates infant in an altered neurochemical environment.
4. baby is born with elevated neuropeptide levelsl neuroplasticity shifts, and altered epigenetic functions.
5. baby inherits poor cranio-mandibular relationship, perhaps further degraded than mothers by modern diet, which contributes further toward developmental abnormalities.
6. When teeth erupt, traumatic cranio-mandibular dysfunction causes shifts in tonicity of reticular formation, altered neuropeptide levels, shifts in immune function, and alterations in endocrine function, contributing to overt onset of autistic symptoms.

Epidemiological data supports such a theory (Ref). There is also an unstudied but peculiar preponderance of mothers with MS who have children with autism (Ref). Like MS, CYP27B1 has been considered in the etiology of autism (Ref). Both MS and autism are steadily on the rise and multigenerational Vitamin D deficiency is a strong link between the two. It’s possible that the root cause of both MS and autism converge on craniofacial development. The importance of adequate vitamin D in the prevention of MS and other CNS diseases is paramount. It is likely that the majority of MS patients exist somewhere on a spectrum of risk factors involving genetic predispositions to weak bones and sutures, skull base defects, improper craniofacial development, and further susceptibilities to decline from environmental and lifestyle influences.

Stress, Bruxism, and Temporomandibular Dysfunction

Stress is ubiquitous and has many adverse effects on health which can exacerbate many clinical conditions. However, it appears to have an unusually strong bearing on MS disease activity from published studies and anecdotal reports. Studies have found that MS exacerbations tend to follow stressful life events (Ref, Ref, Ref). A two year study found that the number of acute stressors was the most important stress-related figure correlating with MS disease activity (Ref, Ref).

Childhood sexual abuse has been associated with development of bruxing behavior (Ref, Ref). A recent
study linked childhood trauma such as emotional or sexual abuse to MS risk in genetically susceptible people (Ref). Spitzer et al report,

> After adjusting for sociodemographic factors and current depression, patients with MS scored significantly higher in all Childhood Trauma Questionnaire subscales apart from physical abuse and neglect than adults from the general population. Adjusted odds ratios for these types of childhood trauma were higher in the MS group than in controls, ranging from 2.0 for emotional neglect (95% confidence interval = 1.3-3.2) to 3.4 for emotional abuse (95% confidence interval = 2.0-5.7). Although childhood trauma was not associated with the degree of current MS-related disability, patients with MS with histories of physical and/or sexual abuse had significantly higher relapse rates than patients without early-life stress.

Stress has long been considered a major contributor to diurnal and nocturnal bruxism, although formal studies have been lacking. At least one study found a correlation between stress, stress-coping, and current sleep bruxism (Ref). Another study found a relationship between increased stress and diurnal bruxism among Indian IT professionals (Ref).

Bruxism is not a normal behavior and its role in the genesis of temporomandibular dysfunction (TMD) has been somewhat white-washed by the “parafunctional” label attached to it (Ref, Ref). The number of bruxism episodes per night and their duration is highly variable. One study found an average of 24.6 episodes per night (Ref) and the typical duration of an episode is 20-40 seconds (Ref, Ref). Presence of bruxism is associated with above average maximum bite force (Ref). The strongest voluntary jaw clenching force ever recorded was 975 psi (Ref) and nocturnal clenching forces can be up to 6 times greater than those achieved during diurnal clenching.

Not surprisingly, given our biomechanical model for MS, studies have established an association between TMD and MS (Ref, Ref). However, these studies propose that MS-related stress and possibly autoimmunity are contributing to TMD whereas the model presented here proposes the reverse, namely that TMD is contributing to MS progression particularly via bruxing behavior. More specifically, a report of three cases found severe complaints of bruxism in the two weeks following their relevant MS attacks (Ref). Two of these patients had mild and infrequent complaints about bruxism prior to their relapses while the third had no complaints. The authors proposed that the bruxism was triggered by the MS attacks but it may indeed be the other way around.
Protective Effect of Pregnancy

Another peculiar finding in MS patients is reduced disease activity during pregnancy, especially in the third trimester (Ref). Thus, it would appear that pregnancy has a protective role in MS. The biomechanical hypothesis offers a compelling explanation for this finding when one considers the role sex hormones play in cranial suture development and their ongoing health. During pregnancy estrogen levels rise continuously, reaching their peak in the third trimester when they are more than 1000 times higher than normal.
The role of estrogen in skeletal development and maintenance is poorly understood but significant. James et al. write,

Estrogens have been shown to be important in the development and maintenance of the appendicular skeleton [14]. Estrogens have two known nuclear receptors, estrogen receptor (ER) α and β. Both receptors are present in the epiphyseal growth plate, specifically in hypertrophic chondrocytes, as well as adjacent bony tissues [15]–[18]. The mechanisms by which estrogens act locally on the growth plate are poorly understood. It has been proposed that estrogen initiates the pubertal growth spurt by stimulating chondrogenesis and inhibiting chondrocyte apoptosis [19]. Additionally, estrogens are postulated to contribute to growth plate fusion via endochondral ossification, possibly by estrogen-induced vasculogenesis and/or osteoblast invasion [20], [21].

To extend these findings, the authors hypothesized that estrogen signaling also plays a role in mouse cranial suture fusion. The authors continue,

In summation, in this study we sought to correlate estrogen signaling with mouse cranial suture fusion, a process of endochondral ossification [4]. We found that ERα gene transcript abundance temporally coincides with PF suture fusion. Moreover, immunohistochemistry detected ER protein primarily within osteocytes and chondrocytes in cranial suture mesenchyme. Via analysis of ER knockout mice, functional ERα but not ERβ was found to be necessary for normal suture fusion. In vitro cell culture of suture-derived mesenchymal cell (SMCs) suggested that 17-β estradiol (E2) enhanced both osteogenic and chondrogenic differentiation within the PF
suture. Finally, in vivo blockade of ER signaling in the developing calvaria via Fulvestrant inhibited suture fusion and led to severely diminished calvarial osteogenesis.

Estrogen also plays a broader role in overall bone health by aiding in the absorption of calcium (Ref). Also noteworthy is the increase in relapse risk during the three months post-partum, before returning to their normal pre-pregnancy levels. This could be attributed to post-partum stress that contributes to bruxism, counteracting the diminishing protective effect of plummeting estrogen levels. Disease activity eventually returns to normal when estrogen and stress levels return to normal. To further support the role of estrogen in the development of MS, studies show that birth control medication increases the risk of developing MS (Ref, Ref). For women of reproductive age with healthy hormonal systems capable of producing estrogen, birth control medication will decrease estrogen levels and potentially increase the risk of developing MS.

**Obesity and MS Risk**

Numerous studies have linked obesity and an increased risk for developing MS especially in females (Ref, Ref, Ref). The long-established link between IIH and obesity can help us understand why obesity also increases the risk of MS (Ref, Ref, Ref, Ref). It is known that intra-abdominal pressure increases linearly with weight. Documentation by anesthesiologists concerning the problems with administering epidural anesthetics to obese patients reveals that the epidural space has greater fat content and because of the increased intra-abdominal pressure, the epidural veins are larger. Obesity also compresses the extracranial venous outlets and diminishes the diameter of the IJVs (Ref, Ref). Similar compression of the vertebral venous systems during upright posture can occur as well.
Obesity associated IIH is likely caused by a maldistribution of hydrostatic forces with compounding venous factors (Ref). In practice, these changes are caused by reduced spinal compliance and increased venous resistance. The condition can be conceptually illustrated with the CSF HIP. The CSF HIP is a point along the CSF axis where CSF pressure is equal in the upright and supine positions and is usually located somewhere between C7 and T5 (Ref). The CSF above the HIP can be thought of as being suspended from the cranial vault (creating a negative pressure cranially) while the CSF below the point can be thought of as resting on the lower dural sac (creating a positive pressure caudally). If the compliance of the lower dural sac increases, the HIP shifts caudally in the direction of the increased compliance creating a more negative CSF pressure cranially. Vice versa, chronically decreased spinal compliance due to obesity will shift the HIP cranially so that the negative cranial CSF pressure becomes less negative and may eventually become positive. The cerebral capillaries must absorb the added force by dissipating osmotic counterpressure (by absorbing ISF). In these circumstances, the tendency for reduction of capillary diameter could render the system vulnerable to incremental increases of venule hydrostatic pressure from increased venous resistance. This in turn impairs CSF absorption and intracranial CSF volume increases resulting in a state of chronic hypertension. Predilection for PCF crowding in the female skull may predispose women to compression of the dural sinuses with further increases to venous resistance and malabsorption of CSF. In some obese patients, compression of the dural sinuses could be a catalyzing event to IIH onset by creating a feedback loop (Ref).

When weight is lost, spinal compliance improves, venous resistance decreases, and the IIH resolves. Obesity associated IIH is a condition that manifests due to a systemic hydrodynamic imbalance present in early adulthood while the brain still retains much of its youthful composition and requirements. During aging, brain and CBV decrease which would tend to counteract the imbalance behind IIH. With the above considerations, it is clear how obesity can increase the risk of developing MS. Reductions in
spinal compliance facilitate chronic MS pathologies and worsen relapsing courses. Reductions to IJV diameter contribute to greater ICP changes and more forceful venous reflux into cerebral veins. In MS pathologies involving spinal cord displacements, obesity can create conditions for venous stasis in the abdominal region with intensified venous reflux from increased blood volumes and forces due to high body fat.

### Physical Trauma and MS Risk

The relationship between trauma and MS has a long, contentious history for a few reasons. One reason is the isolated medicolegal issues and cases that rule in favor of a link when the majority of the existing literature argues against one. A number of studies have found no link between physical trauma and MS (Ref, Ref). Another reason is that reports of trauma causing MS are largely anecdotal despite many patients insisting that their MS had something to do with trauma they had suffered in the past. A large study from Taiwan found an increased risk of MS following TBI (Ref). It is difficult to explain how trauma can increase the risk of developing MS under the autoimmune paradigm which probably explains the vociferous response from critics to the claim that it can in certain cases.

A small study of eight MS patients found a history of head or neck trauma in seven out of the eight, and possibly all eight (Ref). It was hypothesized that an acquired chiari 0 malformation (cerebellar ectopia) due to trauma may play a role in the genesis of some cases of MS (Ref). This anatomical configuration is not to be confused with the congenital chiari 0 malformation which is defined as a hypoplastic posterior cranial fossa (PCF) without tonsillar descent (Ref). On the genesis of acquired chiari 0 malformations Harshfield writes,
One of the current explanations for cause of cerebellar ectopia and the Chiari 0 anatomy (we are now identifying with great regularity) is actually an acquired phenomenon (thus excluding congenital Chiari malformations), occurring as a consequence of trauma/scarring at the cervico-occipital junction. Our recently published paper in the Journal of Brain Injury reported that of our 1200 patients, those with a history of trauma were much more likely to demonstrate cerebellar ectopia, and also, the abnormality was much more conspicuous on upright MRI imaging compared to recumbent MRI imaging.

Normally, the spinal cord is secured by the denticulate ligaments, being perfectly positioned within of the osseous spinal canal. However, loss of any of the three normal curvatures of the spinal axis results in elongation of the osseous canal relative to the length of the spinal cord. As the cord is securely tethered at each vertebral segment, the resultant caudal traction pulls down on the brainstem and cerebellum, hence cerebellar ectopia and concomitant disturbance of CSF migration.

Studies have shown that the degree of tonsillar descent in a chiari 1 malformation does not correlate with the severity of symptoms. Since congenital chiari 0 malformations can be symptomatic and cause syringohydromyelia with little or no tonsillar descent, it would appear that disturbance of CSF pulsations appears to be the key mechanism leading to symptoms and possibly disease. Furthermore, congenital chiari 0 and chiari 1 malformations both demonstrate undersized posterior cranial fossas (PCF) and crowding. An undersized PCF is more common in women than men, with one study finding a female to male ratio of 3:2 for CM1 (Ref). Much like other obstructions at the craniocervical junction, crowding in the PCF and other parts of the skull will tend to amplify the mechanical forces acting on the brain during

<table>
<thead>
<tr>
<th>Years Physical Trauma Present</th>
<th>Description of MS Image Pathology</th>
<th>Current Symptoms</th>
<th>Years Physical Trauma Present</th>
<th>Description of MS Image Pathology</th>
<th>Current Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Two periventricular MS lesions proteinosing corpus callosum from lateral ventricles into adjacent brainstem. Lateral ventricle effaced side (Seg 7).</td>
<td>Loss of vision left eye — optotypy left eye. Loss of muscle strength both legs. Wheelchair bound.</td>
<td>9</td>
<td>One lesion posterior to left occipital horn. Intermittent edema around same ventricle. Peri-ventricular lesion.</td>
<td>Right arm numbness, frontal numbness. Numbness from mid-finger to right shoulder- extending to right fingers.</td>
</tr>
<tr>
<td>2</td>
<td>Occipital horn hydrocephalus also per-ventricular sclerosis.</td>
<td>Memory problems, sleep apnea, Malady and bowel incontinence, impotence, visual difficulties, fatigue.</td>
<td>11</td>
<td>Subtle lesion on flair axial study at first lateral ventricle, peri-ventricular interstitial edema. Possible second ML lesion adjacent occipital horn.</td>
<td>Tingling numbness left shoulder. Blurred vision-left eye. Visual blurring after exercise.</td>
</tr>
<tr>
<td>21</td>
<td>Solitary MS lesions adjacent to left occipital horn and peri-ventricular interstitial edema anterior horns.</td>
<td>Transient episodes of kilodegree vision, numbness left hand, impaired hearing. Weak leg brace to diminish falling. Severe loss of right foot. Severe right pain control. Loss of the sense control.</td>
<td>1</td>
<td>Periventricular MS spanning lesion superior to right occipital horn. Complete small peri-ventricular lesion. MS lesion adjacent to left lateral ventricle midway in AP direction. Peri-ventricular interstitial edema.</td>
<td>Loss of sense control lower legs. Wheelchair bound. Fatigue.</td>
</tr>
<tr>
<td>8</td>
<td>Multiple periventricular MS lesions radiating off lateral ventricles. Multiple periventricular lesions.</td>
<td>Backaches, headaches, syncope to the face. Lack of energy 3 to 7 years old. Sleep, a kid. Gets many sudden times in occult.</td>
<td>27</td>
<td>Multiple periventricular lesions, pronounced hydropathies of the occipital horns of the lateral ventricles with accompanying mass effect.</td>
<td>Optic amnesia, severe vertigo, nausea and vomiting, visual agnoses, stabilizing below walking.</td>
</tr>
</tbody>
</table>

Damadian RV, Chu D. The possible role of crano-cervical trauma and abnormal CSF hydrodynamics in the genesis of multiple sclerosis. 2011;
Extensive investigation by Harshfield and others into the causes of post-whiplash migraines clearly implicates C1/C2 hypermobility as the root cause behind a constellation of neurological signs and symptoms. From “The Craniocervical Syndrome and MRI”,

How can a whiplash injury to the craniocervical junction and upper cervical spine cause incapacitating migraine headaches and a host of disparate neurological complaints and findings? How can we explain the success of the C1-C2 transarticular fixation/fusion procedure in this clinical context?

The vertebral artery may play a key role. This study has demonstrated the association of CCS and lateral ligamentous instability at C1-C2 due to whiplash injury to the alar and/or transverse ligaments. Furthermore, approximately 25% of these patients also exhibit posttraumatic cervicomедullary/vertebral artery compression due to CTE and C1 CS.

Migraine headaches are a vascular phenomenon. Postwhiplash lateral ligamentous instability induces repeated stretching of the vertebral arteries as they travel out of the transverse foramen of C2 and C1 and over the arch of C1 before entering the posterior fossa [9, 34, 35, 55]. This irritative phenomenon may initiate the cascade of vascular headaches. In the clinical case of CTE and C1 CS, both the vertebral artery and the cervical spinal cord-brainstem junction are compressed during neck movement, further contributing to transient vertebral artery dysfunction.
The relevance to MS here is that any resistance to CSF migration or reductions to spinal compliance will redistribute hydrodynamic forces stemming from cranial bone deflection away from the spinal subarachnoid space and onto cerebral capillaries. Recall that in our hydrodynamic model of CSF physiology, intraparenchymal pressure (ICP) is mainly a function of cerebral capillary pressure and that increases to ICP are not caused by an addition of volume into the cranial cavity but from the force required to dispel the additional volume. Also recall that the spinal CSF space can compensate for 30-80% of cranial pressure increase owing to the distensibility of the spinal dura and displacement of CSF from the cranial to the spinal space. Therefore, obstructions at the craniocervical junction facilitate stronger compressive and shearing strains exerted on the brain tissue during skull bone deflection by limiting the compensatory capabilities of the spinal dura. Consequently, there is a net shift of those forces displacing CSF from the intracranial space to those forces displacing venous blood volume (and ultimately to the cerebral venules, capillaries, and brain parenchyma). Moreover, PCF crowding and craniocervical obstructions due to acquired or congenital malpositioning of the cerebellum can predispose the dural sinuses to compression during cranial contraction (ala obesity associated IIH). Thus, physical trauma does not pose an explanatory problem for this biomechanical model of MS as it does for the autoimmune model.

Other studies have sought to establish a possible role between physical trauma and exacerbation of existing MS. Corroborating Oppenheimer’s warnings of neck flexion, Chaudhuri et al. found that cervical hyperextension-flexion injury can exacerbate existing MS (Ref). While an explanation is not forthcoming from the autoimmune hypothesis, these findings make sense in light of the known structural changes in the flanks of the cord, namely the fibrosis originating from the insertion points of the denticulate ligaments. The fibrosis alters the inherent kinematic properties of the spinal cord, and when placed under increased mechanical strain, may cause secondary microvascular damage to the
spinal cord.

**Ehlers-Danlos Syndrome and MS Risk**

The prevalence of Ehlers-Danlos syndrome (EDS) in MS patients is 10-11 times that of the general population (Ref). The anatomical and functional problems in EDS patients reveal why this population group is so much more likely to develop MS. Cranial sutures contain soft connective tissue and collagen fiber bands that play a role in maintaining structural integrity. Case studies of collagen disorders have reported wide open sutures (Ref, Ref). EDS patients have weak bones like MS patients which predisposes them to reduced bone density and mineralization along the sutures (Ref). Craniofacial development can also be affected by the EDS spectrum which can impact the mechanical load exerted on cranial bones from jaw muscles (Ref, Ref).

The genetic hypermobility at C1/C2 in EDS increases MS risk in essentially the same manner as the hypermobility induced by craniocervical trauma. A recent study established a link between hereditary connective tissue disorders and chiari 1 malformation (Ref). The EDS and craniocervical trauma findings confirm that functional cranial settling caused by occipito-atlantoaxial hypermobility (congenital or acquired) is a real phenomenon and could be a significant contributor to MS and risk for neurological disease. Bodily mechanics involving gait and posture in EDS are complex and could also lead to more adverse strains in the upper cervical spine (Ref, Ref). Relatively minor structural or functional imbalances such as a leg length discrepancy could unduly factor in these cases by causing additional head tilt to a

| Table 3: Fractures, BMD, and ultrasound in Ehlers-Danlos patients and normal controls |
|------------------------------------------|------------------|--------|
| Fracture (y/n) | EDS-Danlos | Controls | p Value |
| 18/33 | 9/33 | 0.001 |
| BMD lumbar spine | 0.991 (±0.104) | 1.06 (±0.110) | 0.02 |
| BMD femoral neck | 0.750 (±0.11) | 0.85 (±0.086) | 0.05 |
| BMD trochanter | 0.657 (±0.117) | 0.743 (±0.11) | 0.02 |
| BUA | 71.35 (±176.6) | 92.24 (±203.2) | 0.004 |
| SOS | 1626.9 (±718.1) | 1702.45 (±2) | 0.004 |
| SOS (PGF-150) | 1431.27 (±75) | 1484.12 (±41.6) | 0.028 |
| SOS (LGD) | 1516.12 (±72.3) | 1572.87 (±65.5) | 0.012 |
| BUA (PIN) | 2.77 (±0.18) | 19.34 (±1.5) | 0.024 |
| BUA (UL) | 21.78 (±1.7) | 39.03 (±2.7) | 0.02 |
| BUA (BAQ) | 81.91 (±17.4) | 92.40 (±18.0) | 0.15 |
| SOS (BAQ) | 1675.81 (±73) | 1703.44 (±46.9) | 0.19 |
| BMD lumbar spine | 1.03 (±0.102) | 1.05 (±0.119) | 0.31 |
| BMD femoral neck | 0.84 (±0.091) | 0.81 (±0.09) | 0.81 |

The incidence of MS among the EDS population is 10-11 times greater than the general population. This finding strongly implicates the specific clinical characteristics of EDS as being causitive to developing MS.

EDS patients have poor bone health (like MS patients) which predisposes them to craniofacial abnormalities including poor mineralization along the cranial sutures.
The role of collagen in endothelial dysfunction and inflammation also need be taken into consideration (Ref). In vascular EDS, there is a poor wound healing response within the endothelium related to collagen function. Milewicz writes,

Why would decreased production of type III collagen lead to increased markers of vascular inflammation and platelet turnover? Cutaneous manifestations of vEDS suggest that there is an aberrant wound healing response with loss of type III collagen. Thin, translucent skin with dehiscence of surgical wounds, fistulas, and wide atrophic or papyraceous scars indicate an aberrant response to tissue injury that may also occur when the arterial wall is injured. Tissue injury initiates the wound healing program, a well-described phenomenon involving three overlapping phases: acute hemostasis and early inflammation, subacute proliferative of myofibroblasts and the formation of highly vascularized granulation tissue, and prolonged remodeling and contraction of matrix scar24,25. Thus, injury of an artery may lead to increased levels of inflammatory markers. It is also interesting to note that recent investigations have drawn parallels between traditional cutaneous wound healing and the resolution of intravascular thrombi. Similar to a wound, clot resolution begins with polymerized fibrin at the injury site forming a nidus for recruitment of inflammatory cells, followed by a wave of migrating fibromuscular cells entering the clot to synthesize, remodel, and contract provisional matrix into collagenous scar tissue and vascularization of the clot, and then the resolution into intimal lesions of smooth muscle cells26-28. Since type III collagen is required for a proper wound healing response, it may play a similar role in thrombus resolution.
Therefore, a vascular EDS could significantly exacerbate endovascular inflammation and endothelial dysfunction following MS-related venous reflux. The general effect would be more severe increases to cerebrovascular resistance (Ref).

**Disease Activity Related to Periods of Sleep**

The undocumented fact that many patients (especially RRMS) wake up in the morning with new symptoms, often the first signs of an acute relapse, is a good indication that the MS disease mechanism is most active while the patient sleeps. MS patients frequently experience sleep disturbances and some of these disturbances may well be caused by the injurious mechanisms themselves rather than secondary autonomic dysfunction. A search of the internet produces many examples but a smattering will be provided:

(Ref):

Unfortunately, I had an ms attack 2 weeks ago. **I woke up one morning with only 40% vision in my right eye (this was the same eye that had diplopia in my first attack).** I immediately contacted my ms nurse and went to the hospital for a 3 day course of steroids.

(Ref),

I was diagnosed with ms about a month ago. My first symptom was a sharp stabbing pain in the side of my head right above my ear. I then started getting a general headache and ringing in my ears. I also noticed a throbbing pain in one spot in my right thigh. **I woke up the next morning with the sensation like i just looked into the flash of a camera, and also found out i had developed two severe blind spots in both eyes.**

(Ref),

However, the last couple days I now have numbness spreading down my right arm, where I had none before. **confused I guess this is a new relapse? I'm scared of what I'll wake up with tomorrow morning... and if it will ever go away.** Being a long weekend, there is no one I can call.

(Ref),

**This was very fortunate because just before my appointment was due I woke up one morning numb from the waist down.** It was incredibly frightening. An MRI scan showed lesions - like white spots - in my brain and neck, and I was told this indicated swelling on my nerves that could be MS. The neurologist explained that he would give me high-dose steroids for five days to stop the swelling and only if I had a relapse would he be able to confirm the diagnosis.

(Ref),

In the years since, Frye has remained cognizant of how the disease could affect him and is a bit more strategic in planning for each hunt. **"Sometimes I wake up in the morning and don't feel**
right, so I don’t go hunting on those days,” he explained. He also tries to arrange his Rebif injections to accommodate his hunting schedule, and as often as possible makes sure he has someone hunting with him.

(My last MRI was only 2 months ago, that’s why I’m not in a big hurry to go back to the neurologist. The only meds I take now is Amantadine for the fatigue, which has been very helpful until a few weeks ago when the fatigue started getting stronger than the prescription, I guess. My muscles are sore when I wake up in the morning - my forearms and my inner things - as if they have been spasming during the night. My exercise routine hasn't changed in a while, so I don't think it is that. The jaw pain has been an issue off and on, and I am not sure whether it is stress (dentist has said I’m grinding yes so I wear a night guard) or the trigeminal nerve wreaking havoc (I get both the sore muscles and the electric shocks).

Helpful Links
Website of David Williams: http://essentialms.ca/index.html
Website of Franz Schelling: http://www.ms-info.net