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Time to Revisit Non-Pharmacological Research Approaches to Ameliorate Multiple Sclerosis Symptoms

Bernhard HJ Juurlink

Department of Anatomy and Cell Biology, College of Medicine, University of Saskatchewan, Canada

Corresponding author:
Bernhard HJ Juurlink

bernhard.juurlink@usask.ca

Professor Emeritus, Department of Anatomy and Cell Biology, College of Medicine, University of Saskatchewan, 105 Wiggins Road, Saskatoon, SK, Canada, S7N 5E5

Tel: 250-815-5656

Abstract

Background: The current pharmacotherapies longest in use to treat multiple sclerosis (MS) do not slow progression to disability. The aim of this commentary is to stimulate interest in looking at MS from a new perspective. There is an abundance of evidence that MS is not primarily an autoimmune disease but is a disease where there is first damage to the blood-brain barrier as well as the oligodendrocyte-myelin unit; this damage then elicits an immune response in a subset of people that have an immune system predisposed to attacking myelin-associated antigens. A brief overview is given of the evidence for arterial compliance problems, intracranial compliance problems, venous return problems and hypoperfusion problems in MS.

Conclusions: A rationale is given for the conduction of clinical trials examining the ability of dietary changes, hyperbaric oxygen treatment and approaches to improve venous return as means to ameliorate MS.

Keywords: Non-pharmacological research; Ameliorate multiple sclerosis symptoms; Autoimmune disease; Hypoperfusion

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Introduction

The dominant thread running through multiple sclerosis (MS) research is that it is an autoimmune disease [1]. All the currently approved therapies are aimed at modulating, in one way or another, the immune response to myelin antigens [2,3]. Yet, the immune modulating therapies longest in use (interferon beta-1s and glatiramer acetate), although decreasing MRI-detectable lesions and exacerbations, do not slow progression to disability [4-7]. This ought to suggest that the immune attack seen in MS is not the primary causal factor of the disease but a secondary factor. Indeed, we know from research over a decade ago that early MS lesions and tissue adjacent to growing lesions are characterized by oligodendrocyte and myelin damage as well as activation of local microglia with no or few lymphocytes in the lesion, although lymphocytes are abundant in lesions that are already demyelinated [8-10]. In the words of Henderson *et al.* "The early loss of oligodendrocytes remains a key unexplained feature of active MS lesions" [9]. MS-like lesions that includes blood-brain (blood-retina) barrier breakdown and perivenular accumulations of lymphocytes also occur in the retina in a significant subset of MS patients [11]: the retina contains no myelin. This is additional evidence that MS is not primarily driven by an immune attack on myelin. This is not to say that the immune system does not play a significant role in MS since clearly the majority of allele variants that increase the probability of developing MS are immune-related [12].

Obstructed venous return as a contributor to the symptoms of MS

What is encouraging is that there is beginning to be some recognition that the immune response seen in MS might be secondary to damage to oligodendrocytes and myelin [13-15]. A novel idea recently proposed by Dr Paoli Zamboni and colleagues is that obstructed venous return may play some role in the etiology of MS. Dr Zamboni upon observing altered venous drainage in many MS patients [16,17] that was associated with altered CSF dynamics [18] proposed that "hampered cerebral venous return may contribute to the clinical course of MS" [19]. The Zamboni clinic then proceeded to a small clinical pilot trial where venous angioplasty was used to correct venous return and

concluded "The results, despite the significant rate of restenosis, are encouraging and warrant a larger multicentre double-blinded, randomised study" [20]. So what was the response to this novel concept that venous obstruction may contribute to the MS etiology? A rare few were cautiously favourable, e.g., [21] but the majority of papers published were negative. Here is one of the titles of such papers: "The 'liberation procedure' for multiple sclerosis: sacrificing science at the altar of consumer demand" [22]. The eminent physicist Max Planck once commented: "A scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it". Hence, it is not surprising that new concepts of possible causal factors involved in the etiology of MS are often greeted with great hostility.

Part of the problem that led to this hostile response is that measuring cranial venous return using Doppler imaging is tricky and very operator-dependent with the result that the Zamboni Doppler imaging protocol was not easily replicable. Problems with the diagnostic approach should have led to wide-spread efforts to find better approaches to diagnose venous flow problems. Only a few laboratories took up this challenge. One is the Haacke laboratory who developed novel MRI approaches such as time-of-flight MR angiography (MRA) to assess venous stenosis and 2-dimensional phase-contrast flow quantification to assess blood flow [23]; this study on a large number of control and MS patients showed that a very much larger proportion of MS patients, compared to controls, had stenosis in one or more of their veins draining the CNS and this correlated with lower venous blood flow along the 'normal' routes. Another approach developed was to measure resistance to venous return from the head using cervical plethysmography [24,25]. Here the authors demonstrated that those individuals confirmed as having restricted venous return according to the Zamboni Doppler protocol had an increased resistance to venous return from the head. Increased resistance to venous return will decrease intracranial compliance. Indeed, there are many studies demonstrating decreased intracranial compliance in MS patients, reviewed in ref. [26] and I will not dwell on this further except to state that the most recent study examining the long-term effects of venous angioplasty to correct for impaired venous return concluded that there were significant long-lasting symptom relief for remitting-relapsing MS patients and only transient relief for progressive MS patients [27].

Another interesting feature of the hostile response to the idea that venous angioplasty may ameliorate some of the MS symptoms is an obsession with some of the rare adverse events reported following the angioplasty treatment, e.g., [28]. Of note, some of the adverse effects reported occurred many months following treatment and may have had nothing to do with the angioplasty performed. Such an interest was not seen, for example, when natalizumab (Tysabri) was introduced into clinical trials [29]. Natalizumab is a humanized monoclonal antibody that binds to α4-integrin, thereby preventing movement of immune cells a significant component of the immune response to infection and this feature should have introduced considerable caution into introducing it into the early aspects of clinical trials, but it did not. We now know that natalizumab therapy results in the development of many opportunistic infections, in particular progressive multifocal leucoencephalopathy that occurs in 2 out of every thousand patients [30], of whom 20% die and a further 1/3 become severely disabled.

Diet as a factor in MS

An older idea is that diet may influence MS symptoms. A number of people severely disabled with MS have reported that changing diet and other aspects of their lifestyle have so markedly improved their health that they discarded their wheel chairs [31,32]. These individuals were inspired by the findings of Dr Roy L. Swank. Dr Swank started MS patients at his clinic at the Montreal Neurological Institute on a low fat (particularly low saturated fats) diet and followed them for more than 3 decades. His findings were that 95% of people who strictly adhered to his diet and were newly diagnosed with MS at the time of intervention showed no progression to disability but failure to strictly follow his diet resulted in progression to disability [33].

One would think that such findings, especially published in the Lancet, would initiate a flurry of research in the area of how diet may influence MS progression. A search of PubMed with the search terms 'multiple sclerosis' and 'diet' did not identify any clinical intervention studies examining the effect of diet on MS, except for the studies reported by Dr Swank. A number of epidemiological studies did show up. One showed that increased intake of fatty fish was correlated with decreased MS incidence in a Swedish population [34]. Another epidemiological study showed that increased fish consumption and increased omega-3 fatty acids consumption in an international cohort resulted in a better quality of life in all domains examined and subjects developed less disability [35]. A retrospective study in Italy showed that there was a correlation between high intake of certain foods, for example, wheat-containing products, during childhood and adolescence and the probability of developing MS [36].

If one searches PubMed with the phrases 'multiple sclerosis' and 'dietary intervention' one does come up with a few hits, one of which is a small (23 patients in total) randomized one-year study examining the effects of a low fat diet supplemented with long-chain omega-3 fatty acids [37]. The outcome at 6 months for the low fat diet group was a significantly better Physical Component Scale score that did not quite reach significance at 11 months. There was also a significantly better Mental Health Inventory Scale score at 6 months that was not quite significant at 11 months. The low fat diet group started with a higher baseline Modified Fatigue Impact Scale score and this significantly increased at both 6 months and 11 months whereas there was a non-significant increase seen in the control group. There was also a weak trend in worsening EDSS scores in the control diet group but not the low fat group. Unfortunately, there does not seem to be a follow-up to this therapeutically-promising study. Another paper identified was a case report describing remarkable improvements in a secondary progressive MS patient following major changes to diet along with neuromuscular electrical stimulation and exercise

[38]. A follow-up to this case report is a small open-label pilot trail examining the safety and feasibility of a multimodal intervention using diet, supplements, exercise as well as neuromuscular electrical stimulation [39]. This intervention resulted in a significant decrease in fatigue measures.

There is a surprising paucity of studies in Canada or elsewhere examining dietary changes, or other lifestyle changes, in MS patients. The Multiple Sclerosis Society of Canada lists on its website all research projects funded by them since 1999: there is not one dietary intervention study listed there. Why is this? Is there too much emphasis in research that can lead to intellectual property protection? Having sat on grant review panels of many funding agencies, including the MS Society of Canada, I do know that patentable research is very favourably looked upon.

Another criticism of Dr Zamboni's hypothesis that obstructed venous return may play a role in MS is that it "does not fit into the existing bulk of scientific data concerning the pathophysiology of MS" [40]. The absence of lymphocytes in very early MS lesions suggests that the current 'accepted pathophysiology' of MS also does not fit into the scientific data.

Demonstrating that obstructed venous return is associated with hypoperfusion of the brain, the Zamboni laboratory postulated that such hypoperfusion "could contribute to the known mechanism of virtual hypoxia in degenerated axons" [41]. That hypoperfusion may play a role in MS was suggested almost two decades ago [42]. In 2005, Ge and colleagues published their findings that normal-appearing white matter (NAWM) of MS patients had reduced perfusion that was accompanied by increased blood transit time [43]. A recent study has shown that reduced perfusion and increased mean transit time is present also in white matter lesions [44]. Since there is no evidence that MS patients are characterized by hypotension, the reduced perfusion and increased meant transit time suggests that there is increased resistance to blood flow. Obstructed venous return can contribute to this increased resistance to blood flow. It should be noted that the hypoperfusion findings in NAWM of MS patients have been reported by many other clinical laboratories, reviewed in ref. [45].

Does hypoperfusion give a rationale for Hyperbaric Oxygen Treatment in MS?

Hypoperfusion of NAWM provides a rationale for clinical trials to test for the effects of hyperbaric oxygen therapy in MS patients. Clinics in the USA and Europe have used hyperbaric oxygen therapy to treat MS since the 1970s. Such treatments have turned out to be very controversial since CNS hypoxia did not fit into the MS paradigm of the time. For some of the history of hyperbaric oxygen therapy for MS see Neubauer et al. [46]. Similar to the public interest that followed the idea that venous obstruction can promote development of MS or exacerbate MS symptoms, there was great public interest in the idea that hyperbaric oxygen therapy might ameliorate MS. Public pressure caused the National Multiple Sclerosis Society of the U.S.A. to fund a proper placebo-controlled, double-blinded study where 40 patients were enrolled. Both sets of patients were subjected to 2 atmospheres of pressure, one group was exposed to a 100% oxygen atmosphere while the other group was exposed to an atmosphere comprised of 10% oxygen with the remainder nitrogen [47]. The exposure was for a period of 90 min, 5 days a week for 4 weeks. Improvements in balance, mobility, bladder control and fatigue were seen in 12 of 17 patients and only 1 of 20 control patients. After one year the hyperbaric oxygen-treated patients had less deterioration than the controls. Thus, this study supported the findings of the previous open-label, non-blinded studies.

A PubMed search using the search terms "multiple sclerosis" and hyperbaric oxygen" shows that the last paper published in this area is a meta-analysis of various clinical trials using hyperbaric oxygen treatment [48]. This meta-analysis concluded that there was no clinical benefit to hyperbaric oxygen treatment. It should, however, be pointed out that if one ignores the three reviews listed in this paper and examined only the 16 research and case series reports listed then one comes to a very different conclusion. Of the 16 studies listed, one study showed a positive result with some transient benefits, a second showed transient symptomatic sphincter improvement, a third showed improved symptoms and disability scores, a fourth some benefit in those with mild disease, a fifth showed a minor benefit, a sixth showed reduced number of relapses, a seventh showed transient symptomatic improvement and an eighth showed improved disability scores and symptomology. In other words half of the studies demonstrated some positive therapeutic outcomes with hyperbaric oxygen therapy and half showed no benefit. The logical conclusion from such an analysis ought to be: more carefully controlled studies are warranted, perhaps with patient fractionation.

Whither non-pharmacological MS research?

Can the alternative ideas involving MS etiology such as obstructed venous return, hypoperfusion, diet and other lifestyle aspects fit into the MS pathophysiology as we understand it?

We know the following about MS pathophysiology: 1) An early feature of MS is disruption of the blood-brain barrier (BBB), even in the retina [49]. 2) Disruption of the BBB is an early event occurring even in lesion-free NAWM of MS patients [50]. 3) Early MS lesions are characterized by oligodendrocyte apoptotic changes associated with myelin breakdown, activation of local microglia and absence of infiltrating immune cells [8-10]. 4) This is followed by infiltration of immune cells that then establishes the inflammatory lesion. 5) There is progressive failure to remyelinate that is associated with axon loss [51]. 6) There is a decrease in perfusion of NAWM in MS patients, reviewed in (45), that appears to be associated with hypoxia [52]. And finally, 7) We also know that there are disturbances in cerebrospinal fluid (CSF) dynamics, for example, the volume and velocity of CSF flowing through the cerebral aqueduct both in the cranio-caudal and caudo-cranial direction is much greater in MS patients than controls [53] and net flow, i.e., the difference between the cranio-caudal and caudo-cranial flow is significantly less in MS

patients than in controls [53-55]. These observations can only be explained by a decrease in intracranial compliance associated with a decreased movement of CSF from the subarachnoid space to the dural venous sinuses, see [26] for more details. An increase in the pulsatility of CSF flow through the aqueduct can be explained by more of the arterial pulse pressure wave penetrating the microvessels. Further, a decrease in intracranial compliance can result from: 1) an increase in the hardness of the cerebral tissue, possibly due to MS lesion scarring; 2) a reduction of CSF flowing away from the intracranial compartment to the spinal compartment and/or 3) obstruction of the venous return [26].

A penetration of the arterial pulse pressure wave to the microvasculature might possibly account, at least in part, for the BBB changes seen as well as vessel inflammation, microvascular fibrosis and even oligodendrocyte & myelin damage, see ref. [26] for possible mechanisms. Incidentally, the idea that pulse pressure waves may be involved in MS lesion development is not new. Twenty years ago Professor Franz Schelling proposed that retrograde venous pulse pressure waves might play a role in the etiology of MS [56,57].

So how may obstructed venous return play a role in what we do know of the pathophysiology of MS? If venous return is obstructed this increases resistance to venous return from the brain. Increased venous return will decrease intracranial compliance. Decreased intracranial compliance will result in more of the arterial pulse pressure wave penetrating the microvasculature. Increased arterial pulse pressure waves penetrating the microvasculature will change the CSF dynamics at the level of the cerebral aqueduct as seen in MS patients. This topic is discussed in greater detail in ref. [26]. Clearly Reekers and colleagues [40] are not correct in that obstructed venous return "does not fit into the existing bulk of scientific data concerning the pathophysiology of MS".

What about hyperbaric oxygen treatment? Does it make sense in the context of the scientific data concerning the pathophysiology of MS? Clearly, hypoperfusion and associated hypoxia is becoming accepted as being associated with MS (52), even though the cause of such hypoperfusion may be debated. Hypoperfusion even fits into the obstructed venous return paradigm since increased resistance to venous return by decreasing the pressure differential across the capillary bed will decrease perfusion. Regardless of the cause, if there is decreased perfusion with associated hypoxia, one would expect that hyperbaric oxygen treatment might have some therapeutic benefit.

And how can altering one's diet have therapeutic effects. I will give a few examples. If a problem in MS is arterial pulse pressure waves penetrating the microvasculature as suggested by cerebral aqueduct CSF dynamic changes seen in MS, then one possible cause is a decreased compliance in the arterial walls. Indeed, decreased arterial compliance has been reported for MS patients [58]. Both dietary soy isoflavones [59] and dietary flax omega-3 polyunsaturated fatty acids [60] have been shown to increase arterial compliance, suggesting that these may have some therapeutic benefit in MS.

A second example involves changing the ratio of omega-3 to omega-6 fatty acids in one's diet. The breakdown of the BBB is associated with inflammation. Inflammatory mediators can cause microvessels to fibrose [61,62]; indeed, there is perivascular fibrosis in MS lesions, both in active and inactive lesions [63]. Inflamed endothelia of post-capillary venules also allow entry of activated immune cells [64]. Major drivers of inflammation are the eicosanoids produced upon release of the omega-6 polyunsaturated fatty acid arachidonic acid from the SN2 position of membrane phospholipids by phospholipase A_2 [65]. Omega-3 polyunsaturated fatty acids can also occupy the SN2 position of membrane phospholipids. The eicosanoids produced from omega-3 fatty acids tend to be anti-inflammatory [66]. Thus, increasing the ratio of omega-3 to omega-6 fatty acids in the SN2 position of membrane phospholipids should decrease the probability and severity of inflammation. Membrane phospholipid composition is directly influenced by dietary intake of lipids: hence, one way to have a more favourable omega-3 to omega-6 fatty acid ratio in the SN2 position of membrane phospholipids is to increase the dietary omega-3 to omega-6 fatty acid ratios. As noted above, increased fatty fish consumption (a good source of omega-3 fatty acids) is associated with a decreased MS incidence.

Omega-3 fatty acids may also influence the ability of oligodendrocytes to remyelinate demyelinated axons. As was noted earlier, there is a progressive loss of remyelination of demyelinated axons in MS that is also associated with axon loss [51]. This loss of remyelination may be due to age-related changes of the mononuclear phagocytic lineage of cells [67]. A recent report demonstrates that loss of retinoid X receptor (RXR) function may be responsible for decreased efficiency of myelin clearance and remyelination [68]. The omega-3 fatty acid docosahexaenoic acid (DHA) is a ligand of RXR [69]. Indeed, DHA's neuroprotective action against oxidative stress in retinal photoreceptors is RXR-dependent [70].

Even more intriguing is that RXR is inducible by activation of the Nuclear factor (erythroid-derived-2) like-2 (Nrf2) transcription factor pathway [71]. Activation of the Nrf2 signalling pathway results in the expression of dozens of genes whose protein products decrease oxidative stress, generally either by increasing oxidant scavenging or by decreasing the probability of strong oxidant formation [72,73]; oxidative stress is one of the main drivers of inflammation [74]. This brings us to the third example of how diet may influence MS. Certain phytochemicals found in our diet are potent Nrf2 activators [72,73] and consumption of such dietary Nrf2 activators ought to ameliorate problems that have an underlying oxidative stress and inflammation to them. Indeed, animal experiments have shown promising results, e.g., [75-78]. There are even a few human clinical trials showing promise that consumption of dietary Nrf2 activators can ameliorate problems that have underlying oxidative stress and inflammation components, reviewed in ref [79].

An immediate criticism to the idea that dietary components may ameliorate symptoms of MS is the fact that clinical trials involving

omega-3 fatty acid supplementation have shown no effect on MS as determined by a Cochrane Review [80]. The problem with such clinical trials is that they view the omega-3 intervention in the same manner as a pharmaceutical intervention. In a pharmaceutically-based trial we have a population that does not have the pharmaceutical of interest in their bodies and the trial compares the absence of the pharmaceutical in one population to the presence of a pharmaceutical in another population. We do not have this situation when a population is supplemented with omega-3 fatty acids. All human populations have omega-3 and omega-6 fatty acids in their bodies. The ideal ratio of omega-3 to omega-6 fatty acids in our diet is around 1:1 and the typical Western diet has ratios ranging from 1:10 to 1:30 [81]; hence, a supplementation of omega-3 fatty acid that changes dietary intake of omega-3 to omega-6 fatty acid ratios from, for example, 1:20 to 1:19 would not be expected to have any effect on tissue inflammation. Major changes in diet are required to significantly alter the ratios of omega-3 to omega-6 fatty acids.

Concluding Remarks

There are clear scientific rationales for examining the ability of angioplasty to treated obstructed venous return to ameliorate MS. There are clear scientific rationales for examining the ability of hyperbaric oxygen treatment to ameliorate MS. And there are clear scientific rationales for examining the ability of changes in diet and other lifestyle aspects to ameliorate MS. Certainly the rationales are as valid, and even more so, as those for the currently-approved treatments of MS. I remind the reader that the original rationale for starting clinical trials with interferon β1 was that interferon γ, given to MS patients because it was thought that MS was due to a viral infection, actually aggravated MS; hence, it was thought that since interferon β had in some unknown manner effects opposite to interferon γ, interferon β might ameliorate MS (1). Glatiramer acetate (Copaxone) was originally developed as a myelin protein mimic to induce experimental allergenic encephalomyelitis (EAE) in rodents but rather than inducing EAE it mysteriously ameliorated EAE [82]. As pointed out earlier, natalizumab (Tysabri) was designed to prevent movement of immune cells from the blood to the tissues, thereby crippling the immune response to infection as well as developing cancers, with often disastrous consequences for some MS patients. Fingolimod (Gilenya) downregulates sphingosine-1-phosphate receptors, thereby trapping a subset of lymphocytes within lymph nodes and, thus, unable to enter the CNS [83,84]. Ignored in all this is that sphingosine-1-phosphate receptors are widely distributed throughout the body and not just in lymph nodes [85]. There are a number of case reports describing adverse effects following fingolimod treatment of MS patients, e.g., [86,87].

Finally, we have dimethyl fumarate (Tecfidera). Of the drugs listed, dimethyl fumarate has the best scientific rationale as a treatment for MS. Dimethyl fumarate is an Nrf2 activator [88] and, thus, decreases oxidative stress and inflammation; furthermore, it had previously been used to treat psoriasis. Treatment with dimethyl fumarate does modestly reduce the relapse rate in MS patients but also results in gastrointestinal disturbances in about a third of MS patients with a very small number also experienced leukopenia and lymphopenia. The dose required for dimethyl fumarate to activate Nrf2 is about 50 times larger than dietary Nrf2 activators such as sulforaphane. Perhaps a dietary approach to activate the Nrf2 system would have fewer side effects than the pharmaceutical approach currently used.

I leave the reader with some food for thought.

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