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The Etiology of Multiple Sclerosis: A New and Extended Vascular- Ischemic Model

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Abstract - It is hypothesized that multiple sclerosis is a disease of the cerebro-vascular system. The basic defect is visualized as a wound in the CNS due to a focal hypertension of genetically susceptible vessels which results in vascular injury and the initiation of a series of biochemical and physiological events culminating in an ischemic hypoxia leading to demyelination and a secondary damaging process associated with the immune system:-

Introduction

For approximately the past three decades two hypotheses, independently or in their combined form, have exerted a powerful influence over the field of neurology with respect to the etiology of multiple sclerosis (MS) and the therapeutics based thereon, i.e. the viral and immunologic hypotheses. Several decades of research failed to substantiate these ideas (1, 2). Further substantiation of the failure of these concepts may be obtained from the articles published in *Neurology* 38: **Suppl. 2, 1988: the entire supplement is devoted to the subject:** *Ratio) We for Immunomodulating Therapies of Multiple Sclerosis.*

The vascular ischemic hypothesis as to the etiology of MS **herein presented is designed to integrate present knowledge of the pathophysiology of the disease while obviating the difficulties associated with the current popularly held hypotheses involving viral and/or immunological mechanisms. Also, it provides an explanation for the reported therapeutic successes using hyperbaric oxygenation.**

The proposed hypothesis may explain why there has been, to date, an unending failure to isolate a specific infectious agent-bacterium or virus-from the brains of MS patients that meets Koch's postulates. It provides an explanation for the immunologic changes being viewed as a response to rather than a basis of the MS disease processes (3, 4, 5). The vascular ischemic model along with additional physiologic data also provides a rationale for the low pressure oxygen treatment protocol devised by Neubauer (1).

A prominent feature of the MS lesion is the involvement of the cerebral vasculature: the lesion is primarily perivenule. Therefore it appears logical to examine those properties of the vasculature that may lend themselves to initiating or promoting the eratic MS disease process.

Hypothesis

Cerebral arteriolar dilation: the role of hypertension

The basic hypothesis is that MS is a cerebrovascular-ischemic disease. It is hypothesized that the basic defect is a wound in the CNS due to a focal hypertension which results in vascular injury, edema formation, and an ischemic hypoxia which, in turn, leads to demyelination and a secondary damaging process related to the immune system.

Evidence

Kontos (6) recently reviewed the published evidence related to cerebral arteriolar dilation, their pathologic sequelae, and the biochemical changes associated with acute hypertension. The dilations are not necessarily uniform: they may be preceded by a short constriction. They may be non-uniform with localized dilatations resembling microaneurysm, or dilated segments alternating with constricting segments. Some of the dilatations may be the result of pressures building up due to capillary-venous constrictions discussed below: the weakened portions of the vessels would dilate and resemble microaneurysms. The same pathology also may be associated with or exacerbated by the release of large quantities of superoxide anions from phagocytozing endothelial cells (7).

The dilations are accompanied by marked hyperemia of the brain. Non-uniform dilations may explain, in part, the focal nature of the MS lesion. MS patients do not have hypertension to any greater degree than the rest of the population. However, hypertension as currently understood is not to be misconstrued as being causal to, MS. Insight may be gained into the phenomenon of hypertension involvement if one draws an analogy to low tension glaucoma, a condition in which apparently `normal' ocular tensions produce increased pressure on the optic nerve and retinal vessels to an extent that axoplasmic flow is interfered with and in which retinal perfusion is markedly reduced producing ischemia and tissue hypoxia (8, 9). In such a condition, pressures which are non-pathological in the vast majority of the population are pathologically high for a very low percentage of the population. One can conceive of a similar situation occurring in the cerebral circulation since the eye is really an end organ of the brain bathed in a specialized fluid system, i.e. the ocular fluid secreted by the ciliary processes. Systemic pressures that would not normally be considered hypertensive may causes an arteriolar dilation in genetically susceptible arteries, thromboxane (TxA2) and free radical formation which would result in further vascular injury and edema formation.

Kagan points out that further evidence of the role of an `increased blood pressure' in the etiology of MS may be derived from an understanding of sub-cortical-arteriosclerotic encephalopathy: `...patchy, periventricular long T2 weighted lesions that appeared similar ... in appearance and distribution to ... the lesions of multiple sclerosis in younger patients were frequently seen in elderly individuals. The appearance of MRI scans is part of the continuum called sub-cortical arteriosclerotic encephalopathy, which is called 'Binswanger Disease' if hypertension and dementia are part of the clinical picture. These lesions presumably represent demyelination and/or edema, consequent to chronic ischemia...the older age of these patients and their clinical presentation may often be the only help in differentiating this entity from multiple sclerosis' (personal communication to RAN).

Additional evidence that blood vessel fragility may be an important aspect of MS derives from Swank's (10) study in which he concluded that MS is not confined primarily in or localized to `the CNS: **He observed small cutaneous hemorrhages in 77.4% of female patients observed repeatedly over a 5-9 year period. In 66.7% of these patients, the hemorrhages were spontaneous. `Biopsies of 5 spontaneous hemorrhages, where trauma could be confidently ruled out, revealed extravasated red blood cells infiltrating the deeper layers of the derma and the subcutaneous fat.' Swank goes on to state that `a number of patients have described petechial hemorrhages in large numbers after having their blood pressure taken both under and distal to the cuff.' He notes that the petechial hemorrhages are similar to subcutaneous hemorrhages seen in capillary resistance studies.**

Causes of venule constriction

Thromboxane

Kontos (6) provided pharmacologic evidence that implicates metabolites of arachidonate metabolism via the cyclooxygenase pathway in the production of vascular abnormalities associated with acute hypertension. One of the metabolites of arachido-

nate metabolism is thromboxane (TxA2). TxA2, a very potent venous constrictor, is the primary thromboxane. The TxA2 formed in the arterioles could enter the intercellular space of capillary transudation and diffuse over short distances to the venules.

Edema

TxA2 may also be released in the venules, since it has been shown that the venules are the primary sites of the blood-brain barrier disruption seen during acute hypertension: in fact, the blood-brain barrier is more vulnerable to disruption in venules than in capillaries or arterioles (11).

Curry and Joyner note that endothelial cells comprising true capillaries differ from the endothelial cells of postcapillary venules with the latter being one of the primary sites for regulating permeability (12). They note that `leaky sites' are found in postcapillary venules with changes in endothelial size, shape, and volume modifying exchange areas and diffusion distances. Shasby (13) notes that while endothelial cell shape helps determine transendothelial macromolecule transfer, not all the determinants of shape are known. However, pathways of, acute inflammation are able to alter endothelial macromolecule transfer by reversibly altering endothelial shape: such changes in shape may lie by induced pulmonary edema cell activation involving pathways dependent upon PMN-produced oxidants and pathways independent of these oxidants (13).

The postcapillary endothelial intercellular junctions represent the weakest contacts found in the vascular system (14) with permeability increasing with increases in capillary pressure (12) and as a response to a variety of humoral substances: these induce the opening of the junctions and thereby provide preferential sites for extensive plasma extravasation and diapedesis: these occurrences are noted in inflammation and in response to exposure to toxic substances (14). Humoral agents may modulate permeability through the activation of receptor and non-receptor mechanisms (12). The expression of receptors on endothelial cell surface in response to inflammatory stimuli is an important mechanism for inducing increases in postcapillary venule permeability.

There are other mechanisms (fatty acids, mitosis, free radicals) functioning during the development of the pathologic processes that are also involved in edema production: they will be mentioned in the appropriate ensuing discussions: for the role of fatty acids see ischemia, for mitosis see phagocytosis and for free radicals see partially reduced reactive oxygen species.

The resultant increased venous permeability and subsequent venous constriction could lead to vascular injury on the venous side and culminate in the pathology associated with MS. The hydrostatic pressure resulting from the focal edema would exacerbate constriction-induced tissue ischemia by mechanical compression of the thin-walled capillaries and venules.

Taylor et al. (15) report that ischemic damage to the CNS involves 2 mechanisms: 1. primary ischemic damage due to the ischemic episode itself, and 2. secondary ischemic damage which occurs after reperfusion of the brain subsequent to ischemia. Permanent damage appears to be related to the secondary ischemia (16, 17, 18).

Ischemia, irrrespective of its cause, has a common outcome, an interference with tissue perfusion such that the oxygen supply is insufficient to meet the minimum metabolic needs of the tissue. Prolonged interference with energy-producing mechanisms leads to disruption of cell and tissue oganization, integrity, and function. More extensive damage may occur when the tissue is reoxygenated upon re-establishment of tissue perfusion. Such additional injury is mediated by partially reduced reactive oxygen species (PRROS; superoxide anions, hydroxyl radicals, etc.), a subject that will be discussed in further detail below.

The efficacy of the Neubauer low-pressure HBOT protocol for treating MS, to be discussed below, may be explained, in part, by relatively fewer PRROS being formed during such oxygenation procedures-as compared to what may occur with greater focal oxygen tensions due to HBOT at higher pressures-thereby limiting if not obviating further damage upon oxygenation.

Ischemia also increases tissue concentrations of polyenoic fatty acids, including arachidonic acid (19) which, during the reperfusion, may give rise to TxA2, prostaglandin, and prostacyclin synthesis. In addition to the physiologic effects of their derivatives, the fatty acids themselves are toxic and have been reported to induce edema in brain slices (20).

The vascular-ischemic hypothesis herein developed is complementary to the vascular-ischemic model based on fat embolization proposed by James (21) and may explain the lodging of the

fat emboli in specific locations (see below: phagocytic endothelial cells).

Endothelial cells in vitro and in vivo have been shown to become phagocytic exhibiting a respiratory burst, augmented phagocytic activity, accelerated migration, and cell division (7). Ryan points out that the inefficiency of endothelial cells to kill bacteria may result in these organisms surviving intracellularly where they are also protected from anti-microbial agents and the actions of the humoral and cellular immune systems.

Several factors including low blood flow may contribute to endothelial cells expressing phagocytic activity (7, 12). The intense humorally and mechanically induced venous and capillary constriction could trap circulating fat emboli (17) or microbes which then would be phagocytized by the sensitized cells. It is not known whether pressure sensitivity also induces endothelial phagocytic activity nor is it known if PRROS or thromboxane induce endothelial phagocytosis. Ryan (7) refers to trauma sensitized cardiac valve endothelial cells as undergoing phagocytosis and Davies (22) reports that laminar shear stresses increase the rate of pinocytosis in large vessel endothelial cells. One can conceive of low tension focal hypertension acting as a stimulus to change cerebrovascular endothelial cells: shear stress would be acting to increase endothelial cell turnover (23). Endothelium in which cells are undergoing mitosis are leaky and thus, cell division could serve as another source of fluid escape from the blood-brain barrier.

It is known that phagocytizing endothelial cells could express class 2 antigens and present antigens to lymphocytes. Variability in the handling of the phagoctized microbes may be responsible for the uncertainties and inconsistencies associated with the role of the immune system in MS. In different individuals, diverse microbes (bacteria or viruses) or other particulate antigenic material (myelin or its components) may be presented to lymphocytes as antigens. If the above situation is true, then it helps to explain why there have been reports of viruses isolated from brains (plaques) of MS patients that fail to meet Koch's postulates.

Variability of immune response

The variability of the immune response in MS may be due to the time in which invading microbes, myelin, or other particulate ingested material is presented as antigen which in turn may be related to when antigenic material is released from phagocytizing endothelial cells. Endothelial cells as noted, have inefficient bactericidal mechanism (7). The immune response in MS may not only be due to the formation of PRROS (see below) but also to the chemotaxis associated with them, the variability associated with different types of antigens that may be involved and their presentation to lymphocytes, and the ability of lymphocytes to produce appropriate antibodies.

One of the differences in the pathology of chronic stable and chronic progressive MS could be due to the extent of vascular dysfunction, the relative rates and amounts of PRROS being formed which, in turn, may be related to the extent of phagocytosis by endothelial cells and macrophages and their inherent antioxidant defense mechanisms, the nature of the ingested material, the eventual fate of the ingested particles, the functional state of the immune system, and the degree of neuronal redundancy: factors such as the extent of vascular dysfunction, phagocytic activity, antioxidant defense mechanisms, functional nature of the immune system, and neuronal redundancy may represent some of the genetic bases of the susceptibility to the disease. The progressive disease could be the result of a more extensive involvement of the vasculature, of continued protracted PPROS formation, and the time required for antigen presentation to an immune system-that--may not- be functioning properly. Chataway (2) challenges the traditional concept of MS being a relapsing and remitting disease that may eventually become progressive or may be progressive from the outset by pointing out that advanced imaging and electrophysiologic techniques are demonstrating that MS `never sleeps, it being chronically progressive pathologically, if not clinically'.

Experimental allergic encephalitis

The proposed vascular-ischemic hypothesis is congruent with the fact that experimental allergic encephalitis (EAE), a widely used animal model, is inappropriate for MS; in EAE, myelin destruction results from lymphocytic infiltration whereas in the human phagocytic infiltration follows myelin breakdown (1).

Partially reduced reactive oxygen species

As noted above, Taylor et al. (15) suggests that permanent brain damage appears to be related

to reperfusion secondary to ischemia and it was noted by Ryan et al. (7) that phagocytic endothelial cells exhibit a respiratory burst. Both of these phenomena are related in that they involve the formation of PRROS. Free radicals are also formed during TxA2 formation. In the presence of phagocytized material the endothelial cells produce large quantities of PRROS. PRROS have the potential of inactivating a variety of enzymes thereby disrupting metabolic processes, changes in membrane permeability and fluidity, and damaging blood vessels; the net result is an alteration of the blood-brain barrier and edema formation (12, 13, 24, 25, 26). Although Weiss (27) implies that PRROS do not normally accumulate to any appreciable extent in the extravascular pool, he does acknowledge that `if, however, the inflammatory stimuli are chronically directed against host tissues or are not properly down regulated, neutrophils activate agents that can penetrate all of the host's defenses, as exemplified in inflammatory disease states, the host is ill-prepared to protect itself from this onslaught.' The brain may be particularly susceptible to attack from PRROS since cerebrospinal fluid has little or no iron-binding capacity and disrupted brain tissue undergoes rapid lipid peroxidation, presumably because metals released by cell disruption are not sequestered (28). As noted above (13) inflammatory cells may alter postcapillary venule permeability through PMN-derived oxidants and PMN oxidant independent pathways.

Outside of the CNS, the super-oxide anion, formed during the killing of bacteria by phagacytozing leucocytes, diffuses into tissue fluids and reacts with plasma components to produce a powerful chemotactic substance to normal circulating granulocytes (29). The accumulation of neutrophils at the site of injury and their subsequent activation by ingestion of material from the injury could lead to further injury including increased capillary permeability and edema formation. In the CNS, super-oxide anions resulting from the respiratory burst of phagocytozing endothelial cells could promote or initiate the series of chemical reactions that could lead to lymphocytic infiltration, vacuolization, and periaxial demylination. In actuality, the lymphocytic infiltration is secondary to demyelination resulting from the ischemia-induced hypoxia and possibly from the phagocytizing endothelial cells.

The nature of the MS lesion

The injury to the vascular system resulting from the hypertension, thromboxane and generation of PRROS with the resulting edema formation provides the basis for considering the underlying lesions herein discussed and described as being wounds in the CNS. Ultimately the constant irritation and edema lead to tissue destruction (demyelination) and scar formation.

Focal lesions may vary from 1.0mm to several centimeters. Acute lesions demonstrate phagocytic microglia and perivascular infiltration by lymphocytes and mononuclear cells: chronic lesions are acellular (1).

The sequence of events in the formation of the MS lesion is thought to involve the following: blood-brain barrier disturbance, inflammation followed by edema formation and lymphocytic infiltration, vacuolization, and periaxial demyelination, usually with preservation of the axis cylinder, followed, over a period of years, by gliosis and sclerosis (1).

The above known description of the MS lesion and the currently accepted sequence of events associated with the formation of the MS lesion are consonant with the mechanism herein proposed.

Therapeutic implications

It is the injury to the vascular system and edema formation and the length of time for scar formation that provide the pathophysiological bases for treatment of the disease processes associated with MS by HBOT (1).

There is no direct evidence that MS is either a viral or an autoimmune disease. The use of steroids is designed to decrease inflammation and alter the immune response; immunomodula- for therapy and plamapheresis are based on an immunological etiology of the disease for which there is no direct evidence (1). Chattaway (2) noted: `at present the theoretical basis of treatments which have been used, for example ACTH, steroids and anti-idiotype antibodies, continues to rest on unproven hypotheses concerning possible autoimmune or viral mechanism ... the immune system is abnormal in MS but whether this is the cause or just a result of disorder is unknown. Until one of these ideas is proven, trials of new treatments based on uncertain facts will carry on and the results are likely to reflect this'.

None of these therapeutic modalities is known to alter the course of the disease (1).

In contrast to the immunomodulating approaches to therapy, HBOT is based on the pathophysiology of the disease and it is the only therapy that has been shown to alter the course of the disease (1).

The concept of MS being a wound in the CNS permits several deductions to be made (1): 1. the extrapolation of what has been and is being learned from systemic wound healing to injuries in the CNS; 2. HBOT may be used as a therapeutic modality for early and chronic MS; and 3. the importance of starting HBOT therapy for MS using the Neubauer low pressure protocol.

In systemic wound repair in mammals, one encounters a continuous process involving inflammation, repair, and the regeneration of connective tissue, vasculature, and epithelial covering. In each of these processes oxygen is required. It has been shown that 30-40mm Hg is needed for the following aspects of wound healing; phagocytosis, fibroblastic proliferation, collagen formation, neovascularization, angiogenesis, and epithelialization which, in turn, involves mitosis and cell migration (30).

HBOT overcomes the hypoxia associated with inflammation, edema, and ischemia: these are the very factors that are involved in the pathophysiology of MS. Clinical and animal studies revealed that as a result of its vasoconstrictive actions and simultaneous improvement in tissue oxygen tension, HBOT controls the focal edema of decompression sickness, reduces the raised intracranial pressure associated with global cerebral edema following head and spinal cord injuries and controls the edema in traumatic and non-traumatic syndromes: it reduces the pressure of compartment syndromes, overcomes the ischemia of cardiovascular accidents and assists in the healing of problem wounds, skin grafts, and burns (31). Its twin abilities of reducing edema and providing oxygenation makes HBOT superior to osmotic diuretics and, along with its anti-inflammatory properties and negligible side-effects, suggests that it is superior to and safer than steroids and immunomodulators.

The Neubauer low pressure protocol involves exposing patients, at least at the outset, to pressures no greater than 1.5 ATA: the pressures may be increased gradually over days or weeks with the maximum pressure to be determined by patient response: it may even be necessary to lower the P02 to 1.25 ATA. This protocol was demonstrated to be successful in double-blind and longitudinal clinical studies (1).

The low pressure protocol is supported by the neurophysiologic and CNS wound healing data of Kelly et al. (32) and Gelderd et al. (33), the metabolic data of Holbach et al. (34), the theoretical considerations concerning the formation of PRROS, the in vitro studies of Mehm et al. (35) on fibroblast cell proliferation and collagen biosynthesis, and the systemic wound healing data of Sadeghani et al. (36) **and Farris et al. (37).**

Summary

We view the etiology of MS as being a wound in the CNS which leads to a compromise of the cerebral microcirculation and an ischemic hypoxia of the associated tissues. The wound results from damage done to susceptible arteriolar walls by shear and pressure trauma, the subsequent activation of arachidonate and polyenoic fatty acid metabolism, stimulation of endothelial cells to become phagocytic with these processes producing PRROS, which in conjunction with endothelial cells undergoing mitosis, cause disruption of capillaries-including the normally impermeable blood-brain barrier: there is subsequent edema formation, capillary and venule constriction resulting in an exacerbation of an ischemic hypoxia, followed by a secondary damaging process related to the immune system.

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