CHRONIC / ACUTE CONDITIONS

The Craniocervical Spine and Multiple Sclerosis, Part 1 of 2

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Multiple sclerosis (MS) is a slow, progressive degenerative disease of the brain and spinal cord in which myelin (white matter) breaks down and forms sclerotic plaques. During active demyelination, chemical changes can occur in the lipid and protein constituents of myelin around the plaques, and the concentration of myelin basic protein in cerebrospinal fluid (CSF) may be elevated. Recent studies suggest that axonal injury (involving gray matter) may actually precede demyelination, and that axonal degeneration and brain and cord atrophy, rather than the extent of demyelination, are better indicators of the rate of progression and degree of disability of MS.

MS shows an increased family incidence, suggesting that genetic factors may play a role in susceptibility, and it affects women more than men. Environmental factors also appear to play a role in MS, in that it is much more prevalent in temperate climates than in the tropics. The geographic effect, however, is applicable only when a person lives in one place for the first 15 years, and it does not fluctuate with subsequent relocation after that time period. There are also racial variations in the incidence of MS; for example, Eskimos never get MS, and Asians and most aboriginal people have a much lower incidence.

Despite decades and millions of dollars in research, the cause of MS remains unknown. Evidence to support the viral and immunological theories is lacking, and there is an ongoing debate over the relationship between MS and trauma. While epidemiological studies published in 1991 and 1993 concluded that there was no relationship between MS and trauma, more recent MRI studies suggest that onset of MS may be caused by ischemia, inflammation and injuries of the brain and cord. Congenital or acquired craniocervical syndromes from aging, injury and degeneration of the cervical spine also may play a role in the etiology of MS.

MS and Trauma

The first of the above epidemiological studies followed 170 MS patients and 134 controls for eight years. All episodes of trauma were recorded, and any effects on exacerbation rate and progression of MS were measured. Types of trauma included dental procedures; minor surgery; major surgery; burns; sprains; fractures; and head injuries. The study authors concluded that there was no significant correlation between trauma and MS activity, or the frequency of trauma and the progression of disability.

The second study was conducted by the Mayo Clinic. It used Olmstead County, Minn., population-based records to identify an incidence and prevalence cohort. It then used head injury and lumbar disc surgery cohorts to evaluate the association between mechanical trauma and onset or exacerbation of MS. The population-based cohorts consisted of 225 incidence cases and 164 prevalence cases of definite MS. Researchers then assessed the effect of mechanical trauma in the form of spinal injury or extremity fractures, with regard to precipitation or exacerbation of MS or onset of existing neurological disease associated with an MS-related disability. They found no correlation between peripheral fractures and the onset, exacerbation or final disability of MS.

Next, they examined the cohort of 819 head injury cases, and found that none developed MS during the six months they were followed immediately after the trauma. Finally, they looked at the cohort of 942 lumbar disc surgery cases, and again found no correlation with onset or exacerbation of MS.

The above studies were inappropriate for ruling out a connection between MS and trauma. First, they weren't selective enough in the types of traumas included for analysis. Since MS is primarily associated with degeneration of the lower brain and cervical cord, the focus should be on traumas suspected of causing head and neck injuries, such as motor vehicle accidents and falls. Second, if there is a relationship between trauma, craniocervical syndromes and degeneration of the spine to MS, it probably takes years to develop, not six months.

Rather than trying to conduct meaningful prospective studies, it would be far more cost-effective to perform a retrospective analysis of MS patients who have histories of head and neck trauma and evidence of craniocervical syndromes and degeneration of the spine, and compare it to patients who have MS, but no history of trauma or degeneration.

Hyperintensity Signals in MS and Other Diseases

MS is characterized by disseminated plaques or islands of demyelination and perivascular inflammation. It has predilection for the periventricular areas, optic nerves, and tracts in the midbrain, pons and cerebellum. It also affects the lateral and posterior columns of the cervicodorsal cord. Although it primarily affects the white matter of the brain and cord, MS can also affect the gray matter. In fact, as stated above, recent MRI studies suggest that axonal degeneration may actually precede demyelination. Areas of demyelination and perivascular inflammation show up as increased hyperintensity signals on MRI; axonal degeneration, on the other hand, shows up as areas of hypointensity signals (black holes).

Alzheimer's and Parkinson's diseases, schizophrenia, dementia and manic depression also have a tendency to affect the periventricular and deep white matter areas of the brain, and are sometimes associated with hyperintensity signals in those areas. There is reason to believe that Alzheimer's and Parkinson's diseases and hyperintensity signals may be caused by exitotoxicity from chronic edema and ischemia.

Alzheimer's and, Parkinson's diseases and dementia are also frequently associated with a condition called normal pressure hydrocephalus (NPH), in which CSF volume increases and the ventricles enlarge, but CSF pressure remains normal or only slightly elevated. The cause of NPH is unknown; with Alzheimer's disease, it is attributed to brain atrophy.

Multi-infarct dementia (also called subcortical arteriopathic encephalopathy or Binswanger's disease) is associated with diffuse hyperintensity signals. It is caused by conditions such as chronic hypertension and diabetes. Hypertension pushes excess blood through the blood-brain barrier via increased pressure gradients. Diabetes pulls excess blood through the blood-brain barrier via increased concentration gradients. This results in vasogenic and interstitial edema, and edema that may lead to demyelination, neurodegeneration and hyperintensity signals.

Migraine headaches also have been associated with diffuse periventricular and cerebellar hyperintensity signals. This association is interesting in that migraine headaches are also associated with ischemia-hyperperfusion-edema blood flow patterns. Thus, migraine headaches may also cause demyelination and neurodegeneration as a result of chronic ischemia and edema.

In addition to vascular problems, injury to the blood-brain barrier also can cause edema. However, unless the damage is localized, systemic diseases, vascular problems and injury to the blood brain

barrier cause diffuse hyperintensity signals, similar to those seen in multi-infarct dementia. This is not the case with MS, which has a tendency to occur in particular areas of the brain, especially the periventricular areas. It is possible that the hyperintensity signals in MS and the above diseases may have similar causes. That is, they may be due to chronic ischemia, edema and NPH as a result of craniocervical syndromes and degeneration of the cervical spine.

Ischemia, Edema and the Glutamate Cascade

It has been suggested that edema can cause demyelination. The cause of the edema can be systemic diseases, vascular problems and injury to the blood-brain barrier. In addition to allowing more fluids into interstitial spaces, this particular injury also allows the passage of destructive chemicals, such as enzymes and lactic acid into the brain. This is called cytotoxic edema. Obstruction of the drainage system of the brain, on the other hand, causes interstitial edema and the accumulation of metabolic waste products.

While both cytotoxic and interstitial edema can cause chemical damage to myelin, some researchers have also suggested that edema can damage myelin simply by stretching it. This is interesting because Alzheimer's disease, Parkinson's disease and dementia are often associated with a NPH, in which CSF volume increases and the ventricles enlarge, but CSF pressure remains normal or just slightly elevated. The cause of the NPH is unknown. In Alzheimer's disease, it has always been attributed to brain atrophy. This is no longer true. In fact, some brains return to normal size after shunting to relieve the hydrocephalus. This means they were being compressed by the NPH. Moreover, it means that NPH was the cause, not the result, of the dementia.

NPH enlarges the lateral ventricles and stretches the *corpus callosum*, which forms the roof of the lateral ventricles. The callosum is comprised of myelinated neurons and is frequently associated with hyperintensity signals and atrophy in MS, Alzheimer's and Parkinson's diseases and dementias. Ventriculomegaly may cause demyelination.

Chronic ischemia also may play a role in demyelination. Oligodendrocytes require a lot of oxygen just for maintenance. They need even more for repairs, meaning they are particularly sensitive to slight deceases in blood flow. However, they are typically found at the end of the two arterial supply systems, which makes them susceptible to injuries from ischemia.

In addition to their influence on demyelination, edema and ischemia also release lipid byproducts into the brain. These byproducts are similar to those seen in the glutamate cascade that follows a stroke.

Glutamate is an important excitatory neurotransmitter in mammals. Its cascade is the result of ischemia, which causes depletion of ATP and subsequent failure of the sodium pump. This allows a rapid influx of calcium ions into the nerve, along with the release of glutamate. Excess glutamate stimulates other cells to take in excess calcium and release more glutamate. The excess intracellular calcium combines with other chemicals to form neurotoxic agents that cause additional cell deaths. This process is referred to as "excitotoxicity."

The glutamate cascade also causes phopholipids to break down. This leads to the formation of arachodonic acids, giving rise to free radicals and lipid peroxides that eventually cause blockage of distal blood vessels unrelated to the initial area of ischemia. In many cases, the glutamate cascade causes more damage to the brain than the initial episode of ischemia. Current drug therapies are aimed at arresting the glutamate cascade and excitotoxicity.

MS shows increased myelin basic protein levels in the brain during active demyelination. It has

also been associated with amyloid precursor proteins. The cause of the demyelination is unknown, but, as mentioned above, the latest research suggests that it may be linked to the effects of inflammation, edema or ischemia.

Alzheimer's disease has similarly been associated with amyloid precursor proteins, increased lipid levels, and beta amyloidosis in the brain. Some researchers have suggested the presence of tau proteins in the neurofibrillary tangles point to oxidative stress, i.e., the effects of ischemia, as the cause.

It is possible that the amyloid precursor proteins, increased lipid levels and amyloidosis in Alzheimer's disease are caused by demyelination and neurodegeneration, similar to MS. It is also possible that the demyelination is the result of chronic edema and ischemia, and that demyelination may cause increased lipid levels in the brain that could initiate a cascade of neurodegenerative events, similar to those that follow a stroke.

In summary, it has been suggested that MS and other neurodegenerative conditions of the brain and cord may be precipitated by the effects of ischemia and edema; however, the cause of the ischemia and edema is unknown. Craniocervical syndromes and cervical spine degeneration may lead to chronic ischemia, edema and NPH in the brain and cord, contributing to the development of neurodegenerative diseases such as MS. These possibilities will be discussed further in part two of this article.

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