

Chronic NPH and Degenerative Brain Disease

Michael Flanagan, DC, DABCN

In the first part of this series, we discussed the role of the craniosacral primary respiratory rhythm in cranial hydrodynamics. In the second article, we discussed the role of the accessory drainage system (vertebral venous plexus, VVP) in humans and cranial hydrodynamics during upright posture. In the third article, we discussed the role of the craniocervical spine as the critical link between the cranial dural sinuses and the accessory drainage system, and how craniocervical syndromes may cause blockage or hydrodynamic failure of the cranial dural sinuses and subsequent chronic normal pressure hydrocephalus (NPH). In this last article, we will discuss a possible link between chronic NPH and Alzheimer's (AD), Parkinson's (PD) and other diseases.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) occurs when the volume of CSF increases, but its pressure remains normal or just slightly elevated. NPH causes two problems for the brain. The first is that it increases the pressure acting on the structures that surround the ventricles. The second is that it stretches and enlarges the ventricles. This is important because when the ventricles become enlarged, they stretch the white matter structures that are nearby. For example, when the lateral ventricles become enlarged, the corpus callosum gets stretched. Other white matter structures near the ventricles include the coronal radiata; centrum semiovale; internal capsule; splenium; anterior commissure; posterior commissure; lamina terminalis; cerebral peduncles; and basis pontis. Furthermore, stretching as a result of edema has been shown to damage myelin, and NPH can lead to interstitial brain edema. It is quite possible, therefore, that NPH can damage myelin. This may explain why AD patients often have increased lipid levels in the brain.

Myelin is comprised of lipoproteins. When myelin breaks down, it releases lipids into the brain. Lipids, in turn, degenerate into lipid peroxides and free radicals, which have been shown to play a role in the expression stage of the glutamate cascade following a stroke. Among other things, the glutamate cascade causes blockage of distal blood vessels and advancing cell death. This will be discussed in greater detail later in this article.

The lateral ventricles are surrounded by the hippocampus, caudate nucleus, corpus callosum and fornix, frontal lobe and cingulate gyrus. Nuclei, such as the anterior nuclear group, the dorsal medial nucleus and pulvinar of the thalamus, as well as hypothalamic nuclei, form the floor and walls of the third ventricle. The posterior wall of the fourth ventricle is formed by the vermis of the cerebellum, and the flocculonodular lobe actually invades its interior space.

In addition to the important nuclei and structures that surround the ventricles, cells responsible for the production of neurotransmitters also surround the ventricles, including serotonergic neurons located next to the fourth ventricle and dopaminergic neurons located on the floor and lower walls of the third ventricle. Cholinergic neurons are found throughout the brain, but are especially heavily concentrated in the frontal lobes. NPH, therefore, may affect the production and regulation of

important neurotransmitters, such as dopamine.

Normal pressure hydrocephalus is primarily associated with AD, but as mentioned in the previous article, it has also been seen in conjunction with other diseases, such as Parkinson's disease; multiple sclerosis; schizophrenia; manic depression; lupus erythematosus; rheumatoid arthritis; Padgett's disease; hypertension; hepatic encephalopathy; and diabetes.

In some cases, the cause of NPH is known. Hypertension, for example, damages the blood brain barrier (which leads to edema), and diabetes increases its permeability. In either case, more CSF flows into the ventricles. Certain chemicals and hyperventilation also increase the permeability of the blood brain barrier. On the venous side, diseases such as hepatic encephalopathy increase systemic venous tension and superior sagittal sinus venous pressure (SSVP), thus decreasing the CSF pressure gradient and CSF outflow; this causes an increase in CSF volume. On the physiological side, Valsalva maneuvers and inversion don't cause NPH, but they do cause an increase in SSVP and CSF pressure.

In many diseases such as AD, PD, schizophrenia, manic depression and certain arthritides, the cause of the NPH is unknown. But while the symptoms and the pathology associated with these seemingly unrelated diseases differ, they often overlap. This may be due to the fact that they all involve periventricular structures.

CSF Flow

The design of the lateral ventricles is such that in the upright position, the posterior horns are slightly above the level of the anterior horns. Thus, in the upright position, CSF flows down from the posterior horns and choroid plexus and into the anterior horns. It then exits the lateral ventricles through the interventricular foramen of Monro and enters the third ventricle. CSF leaves the third ventricle through the cerebral aqueduct of Sylvius, which empties into the fourth ventricle. It then exits the fourth ventricle through the foramen of Magendie and Luschka and enters the basal cisterns, which are large dilations in the subarachnoid space found at the base of the brain and around the brain stem. Lastly, CSF leaves the basal cisterns and flows through the subarachnoid space upward and toward the superior sagittal sinus at the top of the head in the upright position.

While moving through the subarachnoid space, some CSF leaves and flows down through perivascular spaces to enter the brain's parenchyma. Interstitial fluids on the other hand, which carry waste from brain metabolism, flow up through the perivascular spaces and into the subarachnoid spaces thus making the subarachnoid and perivascular spaces the lymphatic system of the brain. CSF continues to flow upward through the subarachnoid space to the superior sagittal sinus. From here it is absorbed by arachnoid granulations through one-way valves to enter the cranial dural sinus system. It then exits the brain along with venous blood. It is also interesting to note that CSF also leaves the subarachnoid space along with cranial and spinal nerves.

Blocked Drainage and Chronic NPH

It seems likely that if the drainage systems at the base of the brain are inadequate by design or become obstructed from aging or injury, that it could eventually lead to hydrodynamic failure and chronic NPH. In this type of hydrocephalus, the brain would fill from the bottom up. The structures that would fill first would be the subarachnoid spaces and basal cisterns. The location and size of the cisterns and subarachnoid space gives them a greater capacity to absorb excess CSF. Nonetheless, at a certain volume overflowing may affect structures on the surface of the brain stem such as the medulla,

pons and lower cranial nerves.

After the cisterns become overfilled, the ventricles start to fill up. In contrast to the basal cisterns, however, the ventricles are surrounded by densely packed structures such as cerebellar, hypothalamic, thalamic, and other important nuclei. This limits their capacity to accommodate an increase in CSF volume compared to the cisterns and subarachnoid spaces. When the ventricles fill to capacity they start to compress the structures that are within and around them. When they become overfilled they begin to stretch. Eventually they become enlarged.

The symptoms of NPH may depend on the individual's ability to accommodate an increase in CSF volume in the ventricles, as well as the degree of filling in the ventricles. For example, NPH and AD are both associated with the triad of ataxia, incontinence and personality changes. Of the three signs, ataxia is usually the first. This correlates with the brain filling from the bottom up. That is, shuffling ataxic gait, stooped posture and truncal rigidity are probably the result of overfilling of the fourth ventricle, causing compression of cerebellar nuclei and surrounding structures. Next, incontinence and autonomic signs such as lip-smacking; facial grimaces; staring; pill-rolling; chorionic movements; and athetosis may be the result of compression of thalamic and hypothalamic nuclei, and structures surrounding the third ventricle. Personality changes, such as those seen in schizophrenia, manic depression, and AD, on the other hand, may be due to increased pressure in the lateral ventricles, as well as thalamic nuclei of the limbic brain surrounding the third ventricle. But other signs of tendency toward NPH may include symptoms such as dizziness, migraine headaches and suboccipital neuralgia. These symptoms may be the result of venous hypertension in the suboccipital cavernous sinus and accessory drainage system located just outside the cranium in the craniocervical spine.

NPH is currently associated with enlarged ventricles, but the fissures and sulci remain normal in size. While NPH is considered to be a distinct entity from AD, it may be part of a linear progression of increasing CSF volume and chronicity. In contrast to NPH, AD is associated with enlargement of ventricles, fissures and sulci. Enlargement of these three spaces was previously attributed to cortical atrophy. We know now this is not always the case. There have been cases of NPH with enlargement of the fissures and sulci that have returned to normal size after shunting. This means that the brain was being compressed by the NPH and that it was not atrophied. This led researchers to conclude that shunting should not be denied to patients on the basis of focally dilated fissures and sulci. Unfortunately, not all brains return to normal size after shunting, some are permanently atrophied. This makes it difficult to determine which patients will most likely benefit from shunting.

Hyperintensity Images on MRI

Attempts have been made to identify the best candidates for shunting, according to the presence or absence, and the locations of hyperintensity images on MRI. Some researchers have suggested that periventricular lesions are a more ominous sign than deep white matter lesions and other hyperintensity images and that they are more indicative of a poor prognosis. Other researchers have suggested that while both pre-senile and senile AD show the same cortical and ventricle changes, hyperintensity signals, in general, are more likely to be associated with senile AD. Moreover, some researches maintain that hyperintensity images are a normal variant of aging.

The debate continues over the correlation between the location of the hyperintensity images and the severity of symptoms in AD. What makes the appearance of periventricular and other "deep white matter" hyperintensity images particularly interesting to this discussion, is their proximity to the

corpus callosum, internal capsules and other white matter structures.

If brain edema can stretch and damage myelin, it is conceivable that enlarged ventricles from NPH, and possible interstitial brain edema resulting from NPH, can likewise damage the myelin of the corpus callosum and internal capsule, as well as other white matter structures. This would be especially true in older people whose tissues have lost some of their elasticity. Moreover, as stated previously, myelin breakdown may release lipid byproducts into the brain that could initiate a cascade of degenerative events, similar to the glutamate cascade that follows a stroke.

It is interesting to note that in addition to AD and NPH, multi-infarct dementia (Binswanger's dementia) and migraine headaches are also often associated with hyperintensity signal lesions that are scattered throughout the brain. The cause of the hyperintensity images in multi-infarct dementia is attributed to hypertension, which as previously stated damages the blood brain barrier and causes edema. Migraine headaches, on the other hand, aren't typically associated with hypertension. As stated in the third part of this series; however, migraine headaches may be the result of compression of the vertebral arteries in the suboccipital cavernous sinus. This, in turn, could lead to oxidative stress and subsequent glutamate cascades if the ischemia is severe enough. In either case, hyperintensity signals have been associated with both myelinosis and oxidative stress (ischemia).

The Glutamate Cascade, Oxidative Stress and Neurodegeneration

The latest research in stroke therapy is aimed at developing better neuroprotective drugs to arrest the glutamate (ischemic) cascade, and thus limit the damage to the brain by salvaging surrounding neurons. This is because the threshold for permanent irreparable damage to neurons from loss of blood flow is somewhere around seventy percent. Thus, neurons at the core of the stroke are usually permanently damaged. Surrounding neurons, however, may only lose 50 percent, or even less of their blood flow, and can be saved except for the effect of the glutamate cascade.

The glutamate cascade is the result of ischemia. A lack of oxygen leads to ATP depletion. This causes the sodium pump to fail and cause a rapid influx of ions into the neuron including calcium. The rapid influx of calcium causes the release of glutamate, an excitatory neurotransmitter that increasingly stimulates receptors on other neurons, which in turn opens their calcium gates, causing rapid influx of ions and the release of more glutamate from neighboring cells. The result is neuroexcitotoxicity and cell death from overexcitation and burnout. Excess calcium also causes the formation of enzymes that destroy the cell walls of neurons, resulting in more cell death.

Expression is the final stage of the glutamate cascade. During this stage, phospholipids start to break down. This leads to the formation of arachidonic acids. Arachidonic acids become metabolized and give rise to free radicals and other biochemicals from phospholipid breakdown that promote blockage of healthy blood vessels distal to the initial area of ischemia.

As stated previously, AD is often associated with increased lipid levels in the brain, and advanced AD is associated with neurofibrillary tangles and tau proteins. Among other things, tau proteins have been associated with oxidative stress.) Again, as stated earlier, NPH may lead to the breakdown of myelin and subsequent release of lipids into the brain. This may explain increased lipid levels, amyloidosis, neurofibrillary tangles and tau proteins found in the brains of AD patients. Lipid peroxides could also, in turn, initiate the expression stage of the glutamate cascade, causing additional blockage of blood vessels and oxidative stress. It is possible, therefore, that NPH may be responsible for the increased lipid levels in the brain, myelinosis (such as demyelination), oxidative stress and the subsequent

formation of the tau proteins and neurofibrillary tangles.

Presenile dementia is more likely to show fewer changes in white matter, because the condition is most likely acute and hasn't had time to do as much damage. The victim is also younger and their myelin may be able to better withstand the stretching caused by NPH without breaking down. Presenile dementia, therefore, is more likely to respond to shunting, because even though the ventricles are stretched and the cortex is compressed, there are no secondary degenerative changes from myelin and lipid breakdown. Senile dementia, on the other hand, is probably a slow, insidious process, as a result of the affects of aging and upright posture. Because of the complexity and subtle affects of the structures that line the ventricles, early NPH could easily go undetected.

Glaucoma and Chronic NPH

Chronic NPH shares many things in common with glaucoma. In fact, the optic nerve and eye are actually outgrowths of the third ventricle. It is also interesting to note that the optic nerve attaches to the rear of the eye, and the hyaloid canal extends from the back of the eye at the attachment of the optic nerve, through the vitreous humor to the posterior chamber. Aqueous is produced by the cilia in the posterior chamber, and drains into the anterior chamber, then out through the canal of Schlemm, located in the iridocorneal angle, and into the lacrimal canal. Since CSF leaves the subarachnoid space along with cranial and spinal nerves, it seems reasonable to believe that mammals exposed to prolonged inversion, such as bats, may be able to use the optic nerve and hyaloid canal as an accessory drainage system. This would make the third ventricle and hyaloid canal analogous to the fourth ventricle and central canal, which was discussed in part three.

CSF and aqueous humor are also nearly identical chemically. CSF is drawn from the telea choroidea of the ventricles by osmotic pressure gradients. Aqueous humor is drawn from the cilia of eye by similar processes. CSF and intraocular pressures are also similar. Whereas CSF pressure is about 16-18 mmHg, intraocular pressure is about 18-22mmHg, and both are relatively low-pressure systems similar to lymphatic pressure. One of the causes of glaucoma is stenosis, or blockage of the iridocorneal angle, which contains the drainage system of the eyes, (the canal of Schlemm). Similarly, NPH may be due to stenosis, absence, or blockage of the drainage routes of the brain in the craniocervical spine.

Conclusion

Glaucoma was once a major cause of blindness, but early detection and treatment has dramatically reduced its occurrence. Similarly, prevention, early detection, and treatment of NPH using chiropractic care, medication and surgical shunting may help to decrease the incidence and severity of neurodegenerative diseases of the brain. More importantly, early recognition and treatment of craniocervical syndromes with chiropractic care may help to prevent or limit the incidence and severity of symptoms from chronic NPH.

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Michael Flanagan, DC
Old Tappan, New Jersey

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