IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Introduction:

The human brain (part of the Central Nervous System; CNS) rests within the skull where it is surrounded by a liquid bathe containing cerebrospinal fluid (CSF). Inside the brain are several connected cavities called ventricles. The ventricles also contain CSF. When these cavities become larger than normal a person is said to have ventriculomegaly. Some patients with ventriculomegaly also suffer from increased pressure within the brain from the fluid buildup. This increased Intracranial Pressure (ICP) can cause signs/symptoms that include headache, visual loss, decline in level of consciousness, weakness, and other neurologic deficits. When this happens, the patient is diagnosed with hydrocephalus. A small subset of patients, however, may have enlarged ventricles without elevated intracranial pressure. These individuals have what is termed Normal Pressure Hydrocephalus (NPH) or more specifically Normal Pressure Ventriculomegaly (NPV). The purpose of this Newsletter will be to discuss the clinical entity, etiology and management of idiopathic NPH which has an incidence of up to 5.5/100,000 and which represents one of the few reversible forms of dementia.

Anatomy:

The brain contains four connected fluid filled ventricles (Figure 1):

- Right lateral ventricle
- Left lateral ventricle
- Third ventricle
- Fourth ventricle

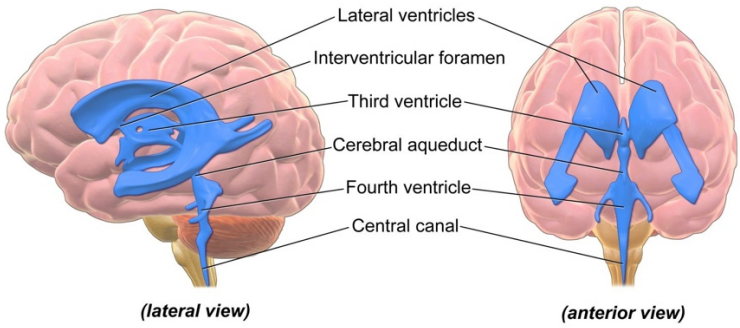

Figure 1: Diagram shows the location of the four intracranial ventricles filled with CSF

Cerebrospinal Fluid (CSF)

In normal adults, the CSF volume is approximately 100-200 cc, with 20% contained in the ventricles and 80% contained in the subarachnoid space in the cranium and spinal cord. The normal rate of CSF production is approximately 20 mL per hour. CSF, a clear, colorless fluid manufactured from blood plasma, is produced by the choroid plexus (located in the ventricles) and from the cells that line the ventricles (ependymal cells) (Figure 2), circulates through the ventricles, the cisterns (large CSF spaces around the brain), and the subarachnoid space (Figure 3) only to be reabsorbed into the blood stream by the brain's arachnoid villi (Figure 4). CSF circulation is a result of cardiac pulsation and pulmonary respiration. CSF is produced at a rate of 0.3-0.4 cc or ml/min (18-25 cc/hour; 430-530 cc/day). Because CSF production in constant, reabsorption is critical for without it, CSF volume would increase resulting in increased intracranial pressure, reduce brain blood perfusion (Cerebral Perfusion Pressure; CPP) and brain dysfunction.

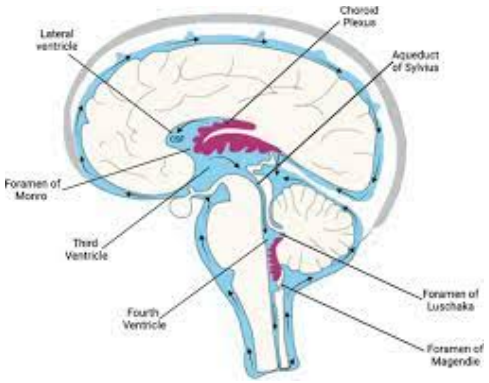

Figure 2: Choroid plexus (pink) produces the majority of CSF.

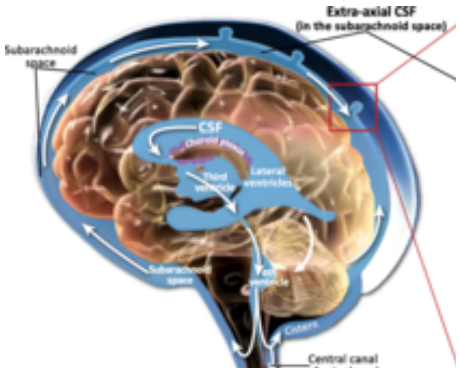

Figure 3: Arrows show how CSF flows in the brain

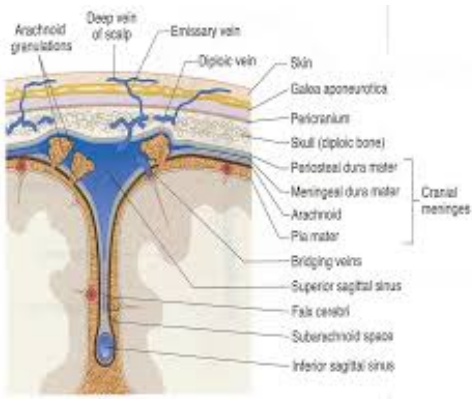

Figure 4: Arachnoid granulations located in the brain. These structures remove CSF from the subarachnoid space and dispose of it in the blood stream.

CSF serves multiple purposes:

1. CSF supports the weight of the brain allowing it to float within the skull. This buoyancy reduces the effective weight of the brain from its actual 1500 grams to about 25 grams.
2. CSF acts like a liquid cushion protecting the brain from damage during head movement.
3. CSF provides the brain with a stable environment helping stabilize temperature and providing a means for cerebral biochemical waste products to be expelled from the body. These waste products diffuse from the brain into the CSF and are removed as CSF is resorbed through arachnoid granulations into venous circulation (Figure 4). A small percentage of CSF also drains into lymphatic circulation.
4. CSF contains glucose, proteins, lipids, and electrolytes, providing essential CNS nutrition.
5. The CSF contains immunoglobulins and mononuclear cells that help fight infections that might develop within the CNS

CSF Pressure:

The CSF that is contained in the ventricles and subarachnoid space of the body exerts a pressure on the surrounding brain and spinal cord. This is termed the Intracranial Pressure (ICP). When a person is lying flat, normal ICP is 7-15 mmHg or 6-25 cm water. At these normal pressure ranges, the brain's ventricles should remain normal is size and the pressure and strain exerted on neurons and white matter tracts in the brain should permit for normal neurologic function. When ICP is elevated above 15 mmHg or 25 cm water, two phenomena develop:

1. Neurons and white matter tracts become compressed and stretched which inhibits their normal function

2. As ICP rises, the cerebral perfusion pressure (CPP) begins to drop. CPP is ideally maintained between 60 and 80 mmHg. CPP can be calculated by subtracting the ICP from the mean Arterial Blood Pressure (mABP) using the equation: CPP = mABP – ICP.

By both automatically adjusting mABP and by adjusting the diameter of the brain's arteries, the body does its best to maintain CPP 60-80 mmHg, however, once the body cannot make further adjustments to mABP and arterial diameter, CPP begins to drop below 60 mmHg, the brain gets less oxygen and nutrition, and it begins to lose its normal function.

What makes ICP increase?

Unlike gas, liquids like CSF are non-compressible. As we add liquid to a container that has a fixed volume and temperature, the number of liquid Particles increases. With more Particles there will be more collisions and a resultant greater pressure within the fixed sized Container.

From the above we see that if we increase Mass (aka: particles of the same size) by increasing the volume of fluid in the brain's ventricles (the Container) we can only keep Pressure constant or below a maximum acceptable physiologic level (60-80 mmHg) by either increasing ventricular size or increasing the rate at which the fluid flows through and is removed from the ventricular system. Because the body cannot significantly increase the rate at which the arachnoid granulations evacuate CSF from the ventricles and because the body keeps making CSF every minute (increased Mass; increased particles; increased collisions), the only way to keep ICP within tolerable levels in a situation where CSF production continues and reabsorption remains constant, is to allow the ventricles to dilate (increase the Container's volume).

The brain tissue can tolerate ventricular enlargement (ventriculomegaly) to only a certain degree. At some point either the ventricles can no longer increase in volume which will lead to increase in intraventricular pressure and reduction in cerebral tissue blood perfusion. Ventricular enlargement also begins to distort white matter tracts and compresses neurons. These physical distortions/stresses eventually cause the neurons and tracts to malfunction which in turn leads to a decline in the brain's ability to generate and/or transmit electrical and chemical information. Neurologic deficits ensue.

Normal Pressure Hydrocephalus:

Clinical Description

Hydrocephalus can be considered communicating or non-communicating. Non-communicating hydrocephalus exists when CSF cannot flow freely from one ventricle to another. In such cases, a blockage exists somewhere within the ventricular system. CSF is produced proximal to this blockage by the choroid plexus, yet it cannot circulate to reach the arachnoid granulations for

reabsorption. This condition can best be compared to a sink that is filling with water from an open faucet while the drain is plugged with debris. The entering water cannot exit to the sewer system. As a result, water collects in the sink until it overflows. Communicating hydrocephalus exists when CSF can flow unhindered from one ventricle to another. In this condition, fluid flows freely but once it reaches the arachnoid granulations it cannot be properly reabsorbed. CSF production therefore exceeds CSF reabsorption and elimination and as the CSF volume increases, the ventricles enlarge due to fluid overload.

NPH is a most typically a form of communicating hydrocephalus in which the cerebral ventricles are enlarged but the intracranial pressure (ICP) is normal (less than 25 cm water). NPH can be secondary or idiopathic. Secondary NPH may develop in relationship to subarachnoid hemorrhage, trauma, infectious meningitis, surgery, carcinomatous meningitis, arachnoid granulation insufficiency, and aqueductyal stenosis. When there is no underlying explanation for NPH, it is often termed idiopathic NPH (iNPH) because the cause for the normal pressure communicating hydrocephalus is unknown. This malady was originally described by McHugh in 1964 (McHugh PR. Occult hydrocephalus. QJ Med. 1964. 33:297-308) and elaborated upon by Adams, Fisher and Hakim in 1965 (Adams RD, et al. Symptomatic occult hydrocephalus with "normal" cerebrospinal pressures: a treatable syndrome. N Engl J Med. 1965. 273:117; Hakim S, et al. The special cliical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. J Neurosci. 1965. 2:307-327).

NPH normally presents insidiously in patients older than 40 years of age and no other illnesses that can explain symptomatology. The classic NPH clinical triad includes:

1. Gait disturbance
2. Dementia
3. Urinary incontinence

Diagnosis generally requires gait disturbance and either dementia or incontinence or both.

<u>Gait disturbance (GD)</u>

GD is usually the first symptom of iNPH. It is described as wide based and shuffling and can be confused with a Parkinsonian gait. Unlike patients with Parkinson's, however, NPH patients do not exhibit limb ataxia. Individuals often describe their feet being "stuck to the ground" (aka: magnetic gait) Patients are unsteady on their feet especially during turning. Arm and leg ataxia is often absent. Initiation of walking or turning is often described as difficult.

GD should consist of two or more of the following:

1. Decreased step height
2. Decreased step length
3. Decreased speed
4. Increased trunk sway while walking
5. Wide based stance

6. Toes turned outward when walking
7. Retropulsion
8. 3 or more steps needed to turn 180 degrees
9. Need to correct 2 or more out of 8 steps when walking

Dementia

Dementia with NPH often presents with impaired memory and slowed thought processes and two or more of the following:

1. Increased response latency
2. Decreased fine motor speed
3. Decreased fine motor accuracy
4. Difficulty with attention
5. Impaired recall for recent events
6. Executive dysfunction
7. Behavioral/personality changes

Urinary Incontinence (UI)

UI is described as non-conscious loss of urine. This must be distinguished from the patient who has incontinence because they cannot reach the bathroom in time to urinate into a toilet.

1. Persistent incontinence without another underlying urologic disorder
2. Fecal incontinence

Radiologic Description (Figure 5)

1. Ventricular enlargement not due to atrophy. Evan's index (ratio of maximum width of the frontal horns to the maximum inner skull diameter) > 0.3
2. Callosal angle $\geq$ 40 degrees
3. Increased periventricular water
4. Flattened gyral tips (vs rounded gyral tips with ex vacuo hydrocephalus)
5. Radionucleotide studies are not reliable for diagnostic purposes

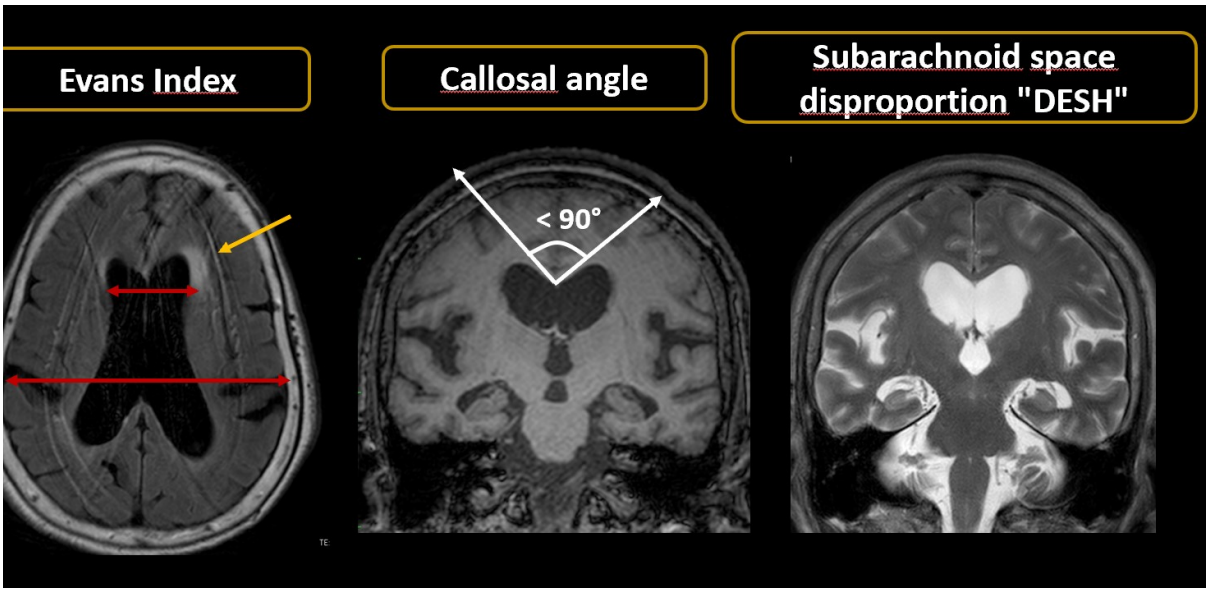

Figure 5: MRI image (left) shows Evan's Index measurements (red arrows), periventricular signal changes (orange arrow); MRI image (center) shows callosal angle; MRI image (right) shows flattened gyral tips against inner surface of skull

Clinical Evaluation:

There are a variety of ways to evaluate patients to determine if they may have NPH and if they may respond to treatment. No single algorithm is correct. The author's favored approach is the following:

1. Detailed office history and examination regarding gait disturbance, thought disturbance and urinary incontinence. Exam must also rule out myelopathy and primary cerebellar dysfunction (limited appendicular ataxia)
2. Detailed history regarding prior strokes, CNS infections, head injuries, therapies (radiation, chemo), familial dementias
3. Review of MRI imaging taking note of tonsillar position, aqueductal patency, ventricle size, degree of brain atrophy, other structural anomalies, appearance of rounded vs. flattened gyral tips
4. Parkinson's Disease and peripheral neuropathy ruled out by Neurologist.
5. MRI lumbar spine to rule out lumbar stenosis and neurogenic claudication
6. If a patient is felt to potentially suffer from NPH then:
    a. Obtain formal Dynamic Gait Index (DGI) performed by Rehabilitation/Physical Therapy specialist
    b. Admit to hospital
    c. Insertion of lumbar drain
    d. CSF Lumbar drainage (15-20 cc/hr if tolerated) for 4 days

e. Daily DGI by Rehabilitation/Physical Therapy specialist to document any changes in DGI
f. If DGI improves $\geq$ 7 points then offer surgical treatment.
g. If DGI improves < 7 points then send patient home and discuss clinical course once home with family and patient. If patient continues to improve per patient and/or family then offer surgical treatment with explanation that the patient is less likely to improve than a patient that had a documented $\geq$ 7 point improvement in DGI while in hospital

Treatment:

For patients without NPH it is often prudent to suggest further neurologic evaluation by a neurologist, urologist and Neuropsychologist/Neuropsychiatrist in search of other potentially treatable causes for their symptoms. For those patients without clear underlying disease and for those with mild NPH, it is often useful to have these individuals pursue more intensive physical therapy and gait training. This non-surgical approach often provides an individual with satisfactory improvement while avoiding more invasive procedures. When patients meet all of the above criteria and want to pursue more definitive therapy the author generally recommends placement of an MRI compatible programmable cranial ventriculoperitoneal shunt (Figure 6). If possible, the peritoneal end of the shunt is usually inserted using laparoscopic techniques by a General Surgeon. Once placed, shunt settings can be magnetically adjusted over time based upon signs, symptoms, and ventricular changes on repeat imaging studies. Titration of CSF diversion generally takes time and may change over time. It is generally useful to continue outpatient physical therapy after shunt placement to maximize gait improvement.

When obtaining informed consent from the patient and/or family/guardian it is critical that the surgeon clearly explain the risks of the procedure which, while generally cumulatively less than 5% include (but are not limited to):

Stroke
Death
Brain injury
Peritoneal content injury
Pulmonary injury/effusions (if placing distal end of shunt into pleural cavity)
Infection (necessitating shunt removal)
Wound dehiscence (necessitating shunt removal)
Delayed hernia formation
Shunt malfunction
Delayed subdural hematoma formation
Headache

In addition to the above, all patients and family must be made aware that even correctly diagnosed and treated NPH may not respond to CSF diversion. They should also be aware that

treatment of NPH is aimed at lifestyle improvement. Patients should not be expected to improve to unrealistic levels of function. Unlike other types of hydrocephalus, treatment of NPH elective, is not generally lifesaving, and should be viewed as life enhancing.

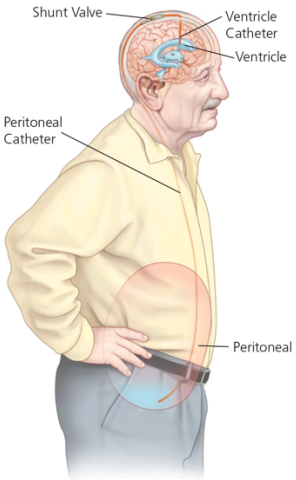

Figure 6: Drawing showing patient with right frontal ventriculoperitoneal shunt in place

<u>The Conundrum of Hydrocephalus Despite Normal Pressure</u>:

After reading the above, the reader understands why patients with abnormal CSF reabsorption would develop increased ICP and ventriculomegaly/hydrocephalus. The reader, however, must at the same time wonder how a condition like NPH can exist. How can the ventricles enlarge, why would they enlarge, and why would they stay enlarged if the pressure within the ventricles is normal or low? After all, if an individual with previously normal sized ventricles develops enlarged ventricles one would assume this is due to increased pressure in the ventricles from the patient having an excessive volume of CSF placed into a container or too little CSF being reabsorbed. This increased pressure would have enlarged the ventricles to a point where they could not enlarge any further without the patient developing neurologic symptoms from increased pressure and decreased cerebral perfusion and white matter tract distortion.

One explanation for NPH could of course be that the ventricular enlargement seen in such patients is due to loss of brain volume. If brain tissue volume decreases due to injury, cell death, or dehydration (similar to how a sponge shrinks when it is used for a long period of time and/or dries out) then one would expect the ventricles to enlarge due to parenchymal volume shrinkage rather than due to expansile forces within the fluid filled ventricles. This could explain why ICP would remain normal or low even though ventricular size increases (hence: NPH). While volume loss is often associated with ventriculomegaly, such ventriculomegaly does not routinely present with NPH symptoms. Ventriculomegaly/Hydrocephalus from volume loss is separately termed hydrocephalus *ex*

vacuo and it is often seen in individuals as they age or in individuals who have suffered from ischemic/hemorrhagic strokes, traumatic brain injuries or various dementias. While these patients may have neurologic deficits, they do not suffer from NPH and see no improvement from typical NPH treatments.

The cause and mechanism of NPH remains unknown. Current theories include the following:

Genetic Mutations

1. Work performed by Hong, et al. (Hong W, et al. Deletions in CWH43 cause idiopathic normal pressure hydrocephalus. EMBO Molec Med. EMBO Mol Med (2021)13:e13249 https://doi.org/10.15252/emmm.202013249)has shown that "two recurrent heterozygous loss of function deletions in *CWH43* were observed in 15% of iNPH patients and were significantly enriched 6.6-fold and 2.7-fold, respectively, when compared to the general population. Cwh43 modifies the lipid anchor of glycosylphosphatidylinositol-anchored proteins. Mice heterozygous for *CWH43* deletion appeared grossly normal but displayed hydrocephalus, gait and balance abnormalities, decreased numbers of ependymal cilia, and decreased localization of glycosylphosphatidylinositol-anchored proteins to the apical surfaces of choroid plexus and ependymal cells.

2. Morimoto, et al (Morimoto Y, et al. Nonsense mutation in *CFAP43* causes normal-pressure hydrocephalus with ciliary abnormalities (2019). Neurology. 92 (20) e2364-e2374; DOI:10.1212/WNL.0000000000007505) identified a loss-of-function variant in *CFAP43* that segregated with the disease. *CFAP43*encoding cilia- and flagella-associated protein is preferentially expressed in the testis. By knocked out mouse ortholog *Cfap43* using CRISPR/Cas9 technology, these investigators developed *Cfap43*-deficient mice that exhibited a hydrocephalus phenotype with morphologic abnormality of motile cilia.

Abnormal Cerebral Venous Drainage

1. Bateman (Bateman GA. The Pathophysiology of Idiopathic Normal Pressure Hydrocephalus: Cerebral Ischemia or Altered Venous Hemodynamics? American Journal of Neuroradiology Jan 2008, 29 (1) 198-203; **DOI:** 10.3174/ ajnr. A0739) has suggested that alterations in superficial venous compliance and a reduction in the blood flow returning via the sagittal sinus contribute to elevation in superficial venous pressure which may cause NPH.