

The Emerging Field of Third Circulation Research

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The meeting has the theme of transcendent leadership in scientific inquiry, patient advocacy, and surgical mentorship. The history of cerebrospinal fluid (CSF) physiology and hydrocephalus presents these themes beautifully. The description of the ventricular system goes back to Galen but it was DaVinci who made the most accurate descriptions of the ventricular system. Key and Retzius in 1875 demonstrated the routes of cerebrospinal flow. This work led to Harvey Cushing's interest in cerebrospinal fluid¹² and his characterization of the circulation of cerebrospinal fluid as the "third circulation." His paper, "The Third Circulation and its Channels" published in 1925, established cerebrospinal fluid physiology as an important aspect of neuroscience.²⁷ He employed Lewis Weed as the neuroscientist in the surgical department at Harvard and says, "these studies led up to Weed's contributions to the development of the arachnoidia and then to the cerebrospinal fluid."^{27, p.12}

This paper will focus on normal pressure hydrocephalus (NPH) in adults, including its patterns and neuroscientific foundations. References are primarily work by the senior author or from collaborations of the authors. It should be noted, however, that pseudotumor cerebri, Arnold-Chiari malformation, syringomyelia, and other disorders may properly be considered disorders of the Third Circulation¹⁸

The era of normal pressure hydrocephalus began with Solomon Hakim's dissertation on a hydrocephalic syndrome in adults with normal CSF pressure. His doctoral thesis in March, 1964 in Bogota, Colombia first described the syndrome and its treatment.²² Over the next 40 years, normal pressure hydrocephalus (NPH) became a controversial topic.^{7,10,14,16,17,20,22,30,39,44,45,46,47} In 2004 and 2005 an international group including neuroscientists, neurosurgeons and neurologists gathered several times to create guidelines for NPH diagnosis and management.³⁸ It was led by Anthony Marmarou from the University of Richmond, Marvin Bergsneider from UCLA, Norman Relkin from Johns Hopkins, Petra Klinge from the International Neuroscience Institute in Hannover, and Peter Black from Harvard. This group's con-

clusions were published in a supplement to *Neurosurgery* in September 2005.³⁸

Two other recent developments have heightened interest in adult hydrocephalus and CSF circulation: increasing pressure from patients to know more about this disease;⁶ and increasing recognition of the general misunderstanding of this condition.⁶ The National Institutes of Health (NIH) recently held a consensus conference in an effort to understand and specify the problems that need to be addressed.³ With an aging population, it is clear that adult hydrocephalus has become an increasingly important topic.

NORMAL PRESSURE HYDROCEPHALUS

Classifications of Hydrocephalus

Two classifications are presently important for hydrocephalus. The first is whether it is communicating or not, that is whether the ventricles connect with the subarachnoid space. This is important because third ventriculostomy may be an effective treatment if there is no communication.³⁴ The second is whether the hydrocephalus is of known or unknown cause. Known causes of normal pressure hydrocephalus include brain hemorrhage of any kind (especially intraventricular or subarachnoid hemorrhage¹³); congenital disorders that become manifest in adult life;⁸ brain tumors and cysts, (especially those of the ventricles, posterior fossa or convexity); head trauma (especially subdural collections⁵), and meningitis including tuberculous meningitis.²⁴

Hydrocephalus Syndromes in Adults

The senior author's experience with over 600 adults with hydrocephalus suggests that there are two major syndrome complexes in this population: high pressure hydrocephalus and normal pressure hydrocephalus. The more dramatic of these two is high-pressure hydrocephalus. This syndrome is characterized by headache, nausea, vomiting, papilledema and obtundation. It may be an emergency and is best treated with either ventricular drainage or endoscopic third ventriculostomy depending on whether it is communicating or not. The normal pressure hydrocephalus syndrome is characterized by gait disturbance, urinary incontinence, and short term memory loss.^{16,39,44}

The gait in normal pressure hydrocephalus has been characterized as an increase in extensor tone in the legs with shuffling described by patients, “as if my feet were glued to the floor.”¹¹ There is also abnormality of arm and hand function but this is not as striking as the gait difficulty. Incontinence is typically restricted to the bladder and may be preceded by urgency. Memory loss is most significant for recent events and is often associated with cognitive slowing.

Brain imaging plays a very important role in the diagnosis of NPH, but its role remains quite complex. Certainly either a computed tomography (CT) scan or magnetic resonance imaging (MRI) must show enlarged ventricles to make the diagnosis, and periventricular low absorption is an important feature. Matsumae and colleagues have done extensive three dimensional measurements of patients with normal ventricles, aqueductal stenosis, high pressure hydrocephalus, and normal pressure hydrocephalus,^{40,41,42}; they have demonstrated that there are significant differences in ventricular, subarachnoid, and brain volumes in these conditions. They have also shown the differences between the normal aging brain and hydrocephalic brain.

Criteria for Diagnosis of NPH

The NPH study group divided the clinical diagnosis of NPH into three categories: “probable” NPH; “possible” NPH; and “unlikely” NPH.⁴⁸

There are four criteria for the diagnosis of *probable* NPH

- 1) Progressive onset
- 2) Large ventricles
- 3) Gait disturbance plus cognitive or urinary disturbance
- 4) CSF pressure 5–18 mm H₂O

The diagnosis of *possible* normal pressure hydrocephalus had

1. Indeterminate onset
2. Ventricular enlargement and also atrophy
3. Gait disturbance or dementia alone; or gait disturbance and incontinence alone
4. CSF pressure unknown or low

Unlikely normal pressure hydrocephalus was characterized by

1. No evidence of ventriculomegaly
2. Signs of increased intracranial pressure
3. No component of the clinical triad of NPH
4. Symptoms were explained by other causes

Diagnosis and Treatment of NPH

In our experience the diagnosis of this condition can best be made by considering the clinical pattern plus the MRI scan. We have demonstrated that clinical criteria - the typical gait disturbance plus ventriculomegaly - predict approximately 80% improvement.⁴³ In this paper, we also showed

that most patients who improved had subtle but definite diminution of ventricular volume. The added test that has been extremely useful in our treatment approach is drainage of CSF from the lumbar canal to assess whether lowering of the pressure will make a difference in walking ability. This is the so-called “lumbar drainage” test and has significantly changed our approach to NPH.⁴⁸

For this test, the patient is brought to hospital in the evening and after an initial physiotherapy evaluation has placement of a lumbar drain at the bedside. The opening pressure is recorded and a closed drainage system is set up whereby 10 cc’s per hour are drained by gravity. Each morning a physiotherapist evaluates the gait using a number of established tests including gait length, width of base, smoothness, and ability to turn. Urinary incontinence and memory are not as easily tested and these tend to be more subjective. We also ask the patient and family whether there is any change in their perception of alertness or general intellectual capacity, based on our observation that an “intellectual cloudiness” is often a problem in people with this condition. In our experience of administering over 200 lumbar drains, we have found that a positive test predicts that shunting has a likelihood of improvement in 85% of cases.

In our treatment approach, this simple test of lumbar drainage has replaced elaborate testing of lumbo-ventricular perfusion or ventricular pressure monitoring, both of which are more invasive and less reliable than lumbar drainage.³²

There are several other tests that have been suggested in the past for the diagnosis of NPH but now might be abandoned. One is the radionuclide cisternogram with indium 111 or other CSF marker.²² The experience of the guidelines group was that this test is generally not helpful in 70–80% of the cases.⁴⁸ If it clearly demonstrates stagnation of CSF in the ventricular system, it is useful to predict a good outcome to shunting. More often, however, it has a mixed pattern which is not helpful. Therefore, we have recommended this test not be used.^{35,37}

There are no other imaging tests that are currently very helpful for diagnosis of this condition. Positron emission tomography (PET) does not have great accuracy, nor does single photon emission computed tomography (SPECT).⁴⁸

Conditions That May Mimic NPH

Several conditions may resemble NPH, the most important of which is Alzheimer’s disease. In patients with this disease the memory deficit is usually much more significant than the gait disorder and there is no slowing of action or thought. There is a more global dementia and there may be seizures, aphasia, or other focal deficits. The CT and MRI show significant atrophy. Parkinson’s Disease may also mimic NPH—the tremor and increased tone with cogwheeling make it distinctive. Multi infarct dementia is a third confounding disorder which usually has much more memory difficulty than gait disorder. The distinction of these condi-

tions from NPH is made more difficult because sometimes they may coexist with it. For this reason a trial of drainage is especially useful in deciding whether to shunt.

A Paradigm for Decision-Making

An example of decision making in a patient is as follows: a patient presents with large ventricles and gait difficulty plus or minus memory loss and urinary incontinence and we do a lumbar drain. If results are positive we shunt, if negative we observe for six months. If the family or patient strongly wishes we may shunt even if the lumbar drain trial is negative based on the assumption that three days may not be long enough to make an accurate assessment in some patients.

Assessing Outcome

There are several scales for assessing shunt outcome,³³ but our experience has been that the best is a simple functional scale (the Black scale):

- Gait
 - 0—normal
 - 1—slight unsteadiness, no falls
 - 2—obvious broad base and short steps
 - 3—substantial daily difficulty with gait including falls
 - 4—difficulty standing
- urine
 - 0—normal
 - 1—mild urgency, no accidents
 - 2—occasional incontinence
 - 3—substantial daily difficulty with incontinence
- memory
 - 0—normal
 - 1—some omissions, able to do work easily
 - 2—remembers 60% of material
 - 3—substantial daily difficulty with memory

Shunt Placement for Idiopathic Normal Pressure Hydrocephalus—the BWH Experience

Over the years we have modified our shunt technique to make the least invasive and most effective system we can.⁴ Presently at the BWH we use a ventriculo-peritoneal shunt with a right occipital burr hole and a midline epigastric incision. The burr hole is made six centimeters (cm) above theinion and three cm to the right of midline. The catheter is inserted 10 cm, aiming toward the nasion. The Codman-Hakim unitized programmable shunt system is tunneled from the scalp to an incision in the midline epigastrium. We set the valve at 120 mm of water and record the opening pressure at this operative setting.

The senior author (PB) has implanted 561 patients with the Codman-Hakim programmable valve since 1988, 260 women and 301 men. An early report outlined the advantages of a variable pressure valve.²¹ The age range of patients was 16–91 years, with median age 68. Of all shunts, 180 were placed in the setting of a brain tumor and 273 for idiopathic

NPH, the remaining were for a variety of other conditions including subarachnoid hemorrhage, trauma, and infection.

For the idiopathic NPH patients 100% had gait difficulty, 72% had a bladder or memory problems as well, and 34% had all three symptoms. The median number of adjustments required to achieve optimum clinical effect was three, with a range of zero to 36. Of all patients shunted 9.8% developed subdural hygromas. It is important to note, however, that more patients with idiopathic NPH developed these than patients with known cause (18% of idiopathic NPH patients). In all but seven cases (1.2%) these subdural collections could be treated by dialing up the shunt pressure, usually 40 points. After a month, the pressure was decreased slowly again if the NPH symptoms recurred. There may be rare sixth nerve palsy if the CSF pressure is lowered too suddenly by a shunt.¹⁹ Shunt malfunction remains an important problem; there were a total of 7.6% of patients who had revisions because of obstruction of ventricular or peritoneal catheter or valve malfunction. These revisions occurred at random periods after shunt placement. The infection rate was 2.4%, almost always with staph epidermidis or propionibacter. The overall improvement rate was 85% using the Black scale noted above to assess improvement.

THIRD CIRCULATION RESEARCH

The data above present some of our clinical experience with idiopathic NPH. Work done in our laboratory over many years or done by us in conjunction with others has expanded our understanding of CSF physiology as well.

CSF Formation and Absorption

Our present belief is that CSF is formed both in the choroid plexus as an ultra-filtrated plasma and in the cerebral parenchyma. It is absorbed by at least three routes. The first is the route into cranial and spinal nerves. In animals this may be the only major CSF absorption route and involves simply filtration through these routes and into the veins and lymphatics of the body. Building on the work of Gordon McComb and others, Griebel in the Black lab demonstrated the importance of cranial and spinal nerve root absorption mechanisms after experimental hydrocephalus in rabbits.³¹ The pathway of CSF egress through nerve root sheaths has not been adequately explored in humans. There is also nearly certain absorption into the cerebral parenchyma by mechanisms that are yet poorly understood. Finally, there is absorption into the arachnoid granulations, which provide a kind of “pop off” system, particularly important in animals that walk on their hind legs.⁹

CSF as a Neuroendocrine Distribution Pathway

A question initially asked by Cushing was whether CSF acted as a pathway for hormone and other metabolite transmission throughout the nervous system. Certainly many neuropeptides can be found in CSF and they may have important neuro-

modulator influences.^{2,49} These include peptides which may change in psychiatric disorders.²⁵ Many years ago we looked at anion transport in CSF as a way of investigating the ability of the system to handle large molecules.³⁶ We have also measured betaendorphin and somatostatin levels² and have determined that there is the possibility that at least some of the symptoms of NPH result from stasis of compounds that otherwise would be “flushed” away. Neuropeptides form an important part of cerebrospinal fluid and their role remains unclear.^{15, 49}

Mechanisms of Hydrocephalus With Known Cause

The nature of the underlying pathology in idiopathic NPH is still unclear. For hydrocephalus following experimental subarachnoid hemorrhage, relative aqueductal stenosis and obstruction to convexity CSF flow were found to be the major problems.¹³ For post-traumatic hydrocephalus, a review of clinical papers suggested that subarachnoid hemorrhage was the most important phenomenon.⁵ Experimental epidural compression was found to cause ventricular enlargement and marked increase in CSF pressure in an animal model.¹ Aqueductal stenosis, especially if it is incomplete, can cause NPH and was difficult to treat before third ventriculostomy became widely used.³⁴ Infection can cause asymmetrical hydrocephalus if the ventricular ependyma becomes involved.²⁴ In an experimental model Conner et al found that there was a very slight gradient between ventricle and subarachnoid space that would provide a driving force for ventricular dilation.²⁶

Present Day Understanding of Hydrocephalus and CSF Dynamics

One of the interesting ways to think about hydrocephalus that has emerged recently concentrates on the pulsatile nature of CSF.²⁸ In the late 1950s and early 1960s, the groundwork was laid for this concept.

Edgar Bering, one of the first participants in the Children’s Hospital Neurosurgical training program, focused his career on this issue and a few other very specific concepts about intracranial dynamics. One of his efforts was to try to determine if the pulsations of the CSF pressure – which he thought were largely coming from pulsations of the choroid plexus – could be the driving force that causes ventriculomegaly. He performed an experiment which causes a kind of communicating hydrocephalus to develop by putting kaolin in the subarachnoid space. He then removed one choroid plexus in one lateral ventricle. His experiment showed that the lateral ventricle that had the bigger pulsations had enlargement despite the fact that the other lateral ventricle had the same mean pressure. The lateral ventricles were connected through the still intact Foramen of Monro, but the pulsations were smaller in the ventricle that did not increase in size.³⁵ One might wonder if this is caused by a difference

in the mean pressure that is just too small to measure, and this perhaps remains a possibility. But Bering was struck at the magnitude of the difference in pulse being quite large and the substantial difference in the ventricular size. This may be relevant for the recent concept that aqueductal turbulent flow may predict a good response to shunt placement.⁴⁸

Of possible importance is the recently published analysis of the height amplitude of the intracranial pressure pulsation by Per Kristian Eide in Norway. He discovered that the correlation between a pulse pressure measured with a special algorithm which he developed of greater than three or four torr over a certain fraction of the time during an overnight intracranial pressure recording appeared to be an effective predictive tool for both predicting who will and who will not benefit from shunting.²⁹ Madsen and Egnor and others have shown mathematical models to explain why this amplitude might be diminished. The attenuation of this amplitude is tuned to the frequency of the heart rate of the patient. Why should there be such a mechanism in the human body? The answer, we think, is that the pulse pressure amplitude is really a surrogate marker for something that is experienced by every cell in the brain and that is the pulsatile shear in the microvasculature.³⁵

If we think of the brain as an enclosed box which has obligate pulsatile input and output, the ability to modulate pulsatility of flow to the level of small vessels is different here than in any other organ because it is the singular organ that is enclosed in a rigid box. Based on this knowledge, we understand that the patients who have the hyper pulse facility benefit from shunting because what shunts actually do is to restore the physiology of the microvascular flow, not the anatomy of the brain. Therefore, to make a better predictive algorithm for the management of our patients, we need to understand pulse changes that occur within a single heartbeat.³⁵

One important implication of this is that our research should perhaps be targeted toward learning more about the dynamics of these pulsations and the dynamics of the response of the brain to the pulsations. A further aspect is the possibility that there will be pharmacotherapy to help the treatment of these conditions.

CONCLUSIONS

In the adult population, idiopathic normal pressure hydrocephalus is an important condition which is poorly understood and poorly treated. It is not diagnosed adequately by neurologists and neurosurgeons, the use of lumbar drainage as a predictive test is not widespread, and fixed-valve shunts are often the only shunts used, leaving clinicians with a high incidence of subdural collections. With present technology we can potentially change this and create an important method of preventing some of the devastation of aging. Moreover, an increase in third circulation research may unlock some of the mysteries that have long eluded neuroscientists in this important area.

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