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Review

Intracranial pressure and ventricular expansion in hydrocephalus: Have we been asking the wrong question?

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Abstract

The force that enlarges the cerebral ventricles and deforms the brain in hydrocephalus remains unclear. It is still widely thought to be elevated intraventricular pressure developing behind an obstruction to the flow of CSF. This view has led to the prediction that a large pressure difference should exist between the ventricles proximal to the obstruction and the subarachnoid space of the cerebral convexity distal to the obstruction. Yet measurements have shown consistently that such transmantle pressure differences are either small or absent. We propose a theory that reconciles the view that hydrocephalus is caused by obstruction to the flow of CSF with the observed absence of large pressure gradients across the cerebral mantle. Obstruction to CSF flow produces only a small pressure gradient — usually less than 1 mm Hg — that is sufficient to overcome the added resistance to flow and thereby to balance the absorption of CSF with its production. This mini-gradient is the effective force that initiates and sustains ventricular enlargement. It can coexist either with high or with normal intracranial pressure. The level of intracranial pressure is determined by the efficiency with which increments of ventricular pressure are transmitted through the parenchyma to the outer surface of the brain. In the presence of a rigid skull some transmission is required by basic laws of Newtonian mechanics. The efficiency of transmission depends primarily on the elastic properties of the brain. If the brain is relatively incompressible, transmission is efficient and high intracranial pressure is required to maintain the mini-gradient between the ventricles and the subarachnoid space, resulting in tension hydrocephalus. If the brain is more compressible, the parenchyma attenuates any increase of intraventricular pressure, reducing transmission to the outer surface. Intracranial pressure need not rise above normal levels to maintain the mini-gradient, leading to normal pressure hydrocephalus. The theory explains why tests measuring CSF resistance have limited diagnostic usefulness in hydrocephalus. It also predicts that very small stresses are sufficient to produce large deformations of the brain if these are allowed to occur slowly.

Keywords: Hydrocephalus; Intracranial pressure; Tension hydrocephalus; Normal pressure hydrocephalus; Brain biomechanics; Brain elasticity; Poroelastic model of brain

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1. Introduction

Both experimental and clinical hydrocephalus are often associated with symptoms of increased intracranial pressure accompanying ventricular dilatation. It is widely assumed that the elevated pressure is a direct result of the continued production of CSF behind an obstruction in its flow path from the ventricles to the subarachnoid space. It is also assumed that this increased pressure acting on the ventricular walls causes them to dilate. Adams and Victor's Principles of Neurology [1] states that as a result of "obstruction to the flow of CSF…CSF accumulates within the ventricles under increasing pressure, enlarging the ventricles and expanding the hemispheres."

It therefore appeared "paradoxical" when Hakim and Adams [2] and Adams et al. [3], following earlier reports of Foltz and Ward [4] and McHugh [5], described the syndrome of normal pressure hydrocephalus. Their patients had communicating hydrocephalus and responded to ventricular shunting even though intraventricular CSF pressure was normal. The paradox arose because it was known that the pressure inside an inflated balloon is always higher than the pressure outside it. Adams et al. and Fishman [6] believed that the same principle applied to the thick-walled cerebral hemispheres. Ventricular expansion required the pressure on the ventricular walls to exceed the pressure on the surface of the brain. The elevated pressure of acute hydrocephalus was thus implicitly assumed to reflect the difference between high pressure in the ventricles and lower pressure on the surface of the brain distal to the obstruction. This assumption was later made explicit in many biophysical models of hydrocephalus. High transmantle pressure gradients were either imposed as boundary conditions [7] or emerged as calculated results [8,9] in such models. If a high transmantle pressure difference is needed to produce hydrocephalus, the natural question to ask was: *How can hydrocephalus occur in the absence of elevated intraventricular pressure?*

Several answers were proposed. These have been reviewed elsewhere [10] and will be mentioned only briefly. One answer was that at some point early in the course there was a high transmantle pressure gradient in each such patient, but with the opening of alternative pathways of CSF absorption, the pressure gradient between the ventricles and the subarachnoid space returned to normal. Potential alternative pathways for CSF absorption, studied in a variety of animal models of obstructive hydrocephalus, included traversal of a dilated central canal to gain access to the spinal subarachnoid space [11]; transependymal flow of CSF with absorption by periventricular capillaries and venules [12]; and absorption via lymphatic channels along the olfactory and other cranial and spinal nerves [13]. Another reason for an initially high transmantle pressure gradient to fall was the tension-bearing capacity of the periventricular white matter. If the ventricular walls could not develop increasing tension in proportion to the growth in ventricular radius, transmantle pressure would fall with increasing ventricular size, even in the absence of new alternative pathways for CSF absorption. For example, in a soap bubble, where wall tension remains constant even as the bubble grows, expansion of the bubble is associated with reduction of the transmural pressure difference. Yet another answer was that the range of normal CSF pressure is very wide, and perhaps what appeared to be a normal pressure in a given patient was really a high pressure for that particular individual.

2. Absence of large transcerebral pressure gradients

Observations in both experimental and clinical hydrocephalus have cast doubt on the hypothesis that large transcerebral pressure gradients are required for ventricular dilatation in hydrocephalus. Two early studies detected only small pressure gradients between the ventricles and the periphery of the brain. Hoff and Barber [14] studied four patients with normal pressure hydrocephalus and found that mean ventricular pressure was 1–2 mm Hg higher than mean pressure in the subdural space. When saline was infused into the lumbar subarachnoid space, the pressure difference increased to 2–4 mm Hg as mean intracranial pressure rose to over 30 mm Hg. Conner et al. [15] measured pressure in the lateral ventricles and in the subarachnoid space over the cerebral convexity of cats with hydrocephalus induced by the intracisternal injection of kaolin. At baseline, before treatment, the pressure difference was only 0.2 mm Hg. After kaolin the pressures were measured weekly for 1 month. The pressure difference varied considerably between animals and between measurements in a given animal but increased to 2.5±2.9 mm Hg. The majority of studies, including those done more recently, have shown no detectable transmantle pressure differences. In cats with craniectomy and kaolin hydrocephalus Shapiro et al. [16] measured intracranial pressure (ICP) in the lateral ventricles, cisterna magna, convexity subarachnoid space, brain tissue and superior sagittal sinus simultaneously 4 to 9 weeks after kaolin. No differences in ICP were found among any of the recording sites. Penn et al. [17] performed long-term recordings of ICP in dogs implanted with sensitive pressure transducers in the lateral ventricles, parenchyma and subarachnoid space. The dogs were then made hydrocephalic with cisternal kaolin. Intraventricular pressure initially rose and then subsided. But parenchymal and subarachnoid pressure rose in parallel.

There was no detectable gradient of pressure from ventricles to subarachnoid space. Stephensen et al. [18] implanted pressure transducers in the right lateral ventricle and the subarachnoid space over the cerebral convexity of ten patients with either communicating or non-communicating hydrocephalus. There was no significant difference between the two sites in mean pressure or in the amplitude or waveform of ICP pulsations produced by cardiac contraction or by respiration.

Theoretical calculations based on MRI anatomical and CSF flow measurements also suggest that there need be only a small pressure difference between the ventricles and the subarachnoid space, even in hydrocephalus. The aqueduct of Sylvius, being the narrowest portion of the pathway of CSF flow, offers the most resistance to CSF flow. However, estimates of the pressures required to maintain a steady bulk flow through the aqueduct equal to the rate of CSF production are less than 0.01 mm Hg [19–21]. The pressure required to generate the peak pulsatile flow through the aqueduct during the cardiac cycle is on the order of 0.1 mm Hg [22]. Linninger et al. [23] estimated that the peak difference during the cardiac cycle between pressure in the ventricles and pressure in the intracranial subarachnoid space was 0.08 mm Hg. In a later study Linninger et al. [24] calculated that the pressure difference between the lateral ventricles and the intracranial subarachnoid space throughout the cardiac cycle did not exceed 0.06 mm Hg in a normal subject and 0.18 mm Hg in a patient with communicating hydrocephalus.

It thus appears that even a very small increase in the gradient of pressure between ventricle and subarachnoid space is sufficient to produce ventricular dilatation. The dilatation occurs at the expense of the brain's interstitial fluid and exchangeable intracellular fluid, which are driven into the bloodstream [25]. There is a delicate balance of the Starling forces of hydrostatic and osmotic pressure across the brain capillaries. Any increase in ventricular pressure will be accompanied by an increase in the hydrostatic pressure of the interstitial fluid, particularly in parts of the brain adjacent to the ventricular system [26]. Even a small increase in the hydrostatic pressure of the interstitial fluid upsets the balance of Starling forces and is enough to start the process of absorption of interstitial fluid into brain capillaries, leading to ventricular enlargement. The required increase in ventricular pressure may be below the resolution of the transducers used in the studies cited above. If this is so, the question to ask is not how hydrocephalus can come about with CSF pressure in the normal range, but instead why normal pressure is not present in all cases of hydrocephalus. The question becomes: *What is the mechanism of tension — i.e., high pressure — hydrocephalus?*

3. Satisfying two constraints: CSF pressure in hydrocephalus

Both experimental evidence and calculations made from plausible mathematical models suggest that the intracranial pressure that prevails in a particular hydrocephalic patient is the result of a balance between two conflicting requirements:

First, there is the need to maintain a small, but abnormal difference between the CSF pressures proximal and distal to an obstruction in the pathway of CSF flow. The obstruction may be intraventricular — non-communicating hydrocephalus — or may be in the subarachnoid space — communicating hydrocephalus. This increased pressure gradient is needed to overcome the increased resistance to CSF flow so that CSF absorption can balance CSF production — a statement that is merely a generalization of Ohm's law. The required pressure difference may be quite small. In the kaolin dog [17] the increment was on the order of 0.5 mm Hg or less. Possibly it is somewhat larger in hydrocephalus that develops more abruptly, such as after plugging the aqueduct [27], but this has not yet been measured.

Second, there is the need to allow for the transmission of intraventricular pressure to the outer surface of the brain in the form of radial compressive stress. Some degree of transmission is required by the basic physical laws of conservation of mass and balance of forces on a body in equilibrium when the brain is bounded by a relatively rigid skull that constrains its outward movement. Hakim [25] verified the partial transmission of increments of ventricular pressure to the subdural space on the outer surface of the cerebral convexity in two patients with hydrocephalus. The degree, or efficiency, of transmission depends upon the elastic [25] — or, more specifically, the poroelastic [26] — characteristics of the cerebral tissue. For example, if the brain were absolutely incompressible, any pressure against the ventricular wall would be fully transmitted to the periphery and thus would be matched by equal pressure exerted by the skull on the outer surface of the brain. In contrast, if the brain had the consistency of compressible foam rubber, pressure against the ventricular wall would be "absorbed" by the parenchyma and poorly transmitted to the periphery. Levine [26] developed a model of the brain as a thick spherical shell of parenchyma enclosing a concentric spherical ventricle and bounded by a rigid skull (Fig. 1). The parenchyma was modeled as a three-phase linear poroelastic structure, consisting of a cytoskeletal matrix permeated by incompressible interstitial fluid and by a network of compressible capillary and venous channels. In that model the calculated transmission of ventricular pressure to the outer surface of the brain depended upon the drained Poisson ratio, a measure of brain compressibility, and upon ventricular size. It was given approximately by the formula $T = \frac{3(1-\nu)}{2(1-2\nu)\Gamma^3+1+\nu}$ where T represents the fraction of ventricular pressure that is transmitted to the outer surface of the brain as a result of the poroelastic behavior of brain tissue, ν is the drained Poisson ratio, and Γ is the ratio of brain radius to ventricular radius. From this formula it can be seen that when $\nu = 0.5$ — i.e., when the brain is incompressible — full transmission occurs — i.e., $T = 1$. The dependence of T on the variables ν and Γ is shown in Fig. 2. For lower values of ν, representing more compressible brain parenchyma, the fractional

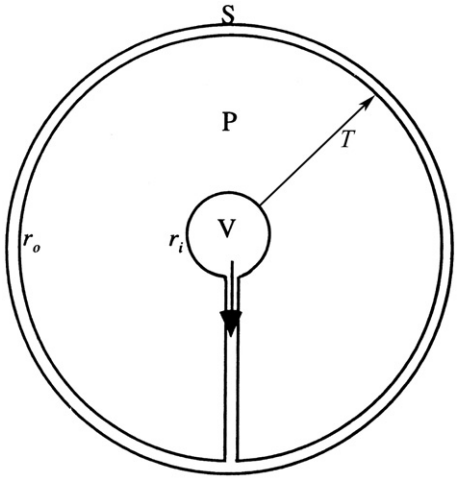

Fig. 1. Section of a spherical model of the brain through a meridian. V is the combined lateral and third ventricles, P is the three-phase poroelastic parenchyma, and S is the skull and dura. The ventricle has radius r_i and the surface of the pia is at radius r_0. The ratio r_0/r_i is the term Γ in the equations of the text. The pia is separated from the dura and skull by the CSF-filled subarachnoid space. The downward pointing arrow signifies the passage of CSF through the aqueduct of Sylvius and fourth ventricle into the subarachnoid space. The arrow labeled T represents the process of transmission of changes in ventricular pressure to the surface of the brain that is a calculated consequence of the model.

transmission decreases. For any given value of v the fractional transmission also decreases with smaller ventricular radius — i.e., larger Γ.

The satisfaction of the two constraints — an abnormal, though still small, pressure difference between the ventricles and the subarachnoid space; and the transmission, at least in part, of changes in ventricular pressure to the outer surface of the brain — can be stated in the form of a simple algebraic equation: $P_v - \left(P_v^n - \nabla p^n + T\left(P_v - P_v^n\right)\right) = \nabla p$, where P_v represents the ventricular pressure that satisfies both constraints; T represents the fraction of ventricular pressure that is transmitted to the outer surface of the brain; and ∇p represents the small pressure gradient between the ventricle and the subarachnoid space distal to the obstruction, which is needed to ensure that CSF absorption equals CSF production. The superscript n refers to normal values prior to the hydrocephalus. The term within parenthesis on the left side represents the CSF pressure in the subarachnoid space. This consists of the normal subarachnoid CSF pressure — the first two terms within the outer parenthesis — and the pressure transmitted from the increase in ventricular pressure — the third term. The equation states that the difference between ventricular CSF pressure and subarachnoid CSF pressure equals the transmantle pressure gradient needed for CSF absorption. The equation can be solved for the ventricular pressure to yield $P_v = P_v^n + \frac{\nabla p - \nabla p^n}{1-T}$.

The dependence of ventricular pressure on the size of the gradient and on the efficiency of transmission of pressure from the ventricle to the periphery is shown in Fig. 3. It is evident that ventricular pressure increases linearly with the size of the gradient ∇p and non-linearly with the efficiency of transmission T. The effects of varying ∇p and T on intracranial pressure can be appreciated by considering two hypothetical cases. First, suppose that an individual with a baseline CSF pressure of 10 mm Hg develops a sudden obstruction of the basal cisterns that requires intraventricular pressure to exceed the subarachnoid pressure distal to the

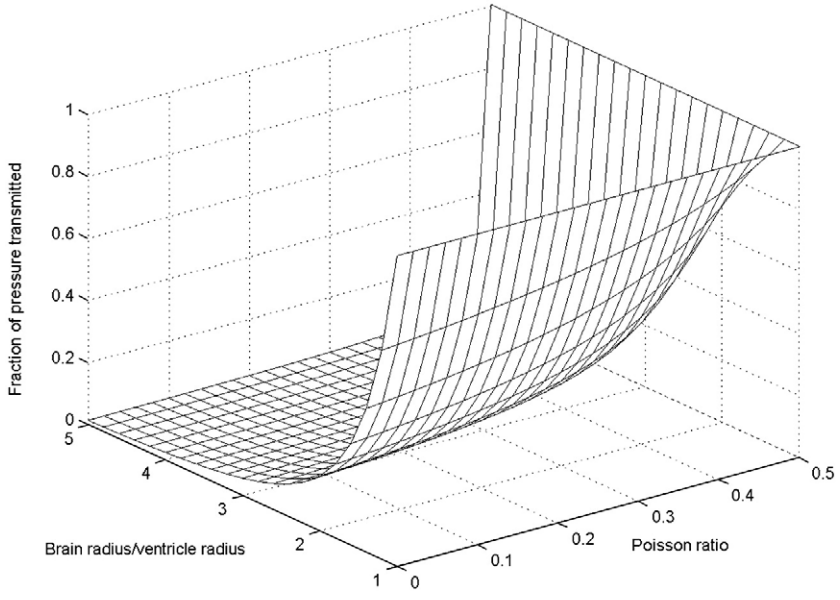

Fig. 2. Fraction of the ventricular pressure transmitted to the surface of the brain calculated from a model of the brain as a rigidly enclosed spherical poroelastic shell [26]. The transmission varies as a function of ventricular radius and compressibility of the poroelastic shell. Transmission is high if the brain is relatively incompressible (Poisson ratio near 0.5) and decreases as the brain becomes more compressible (decreasing Poisson ratio). Transmission also increases with ventricular size (decrease in Γ, the brain radius/ventricular radius).

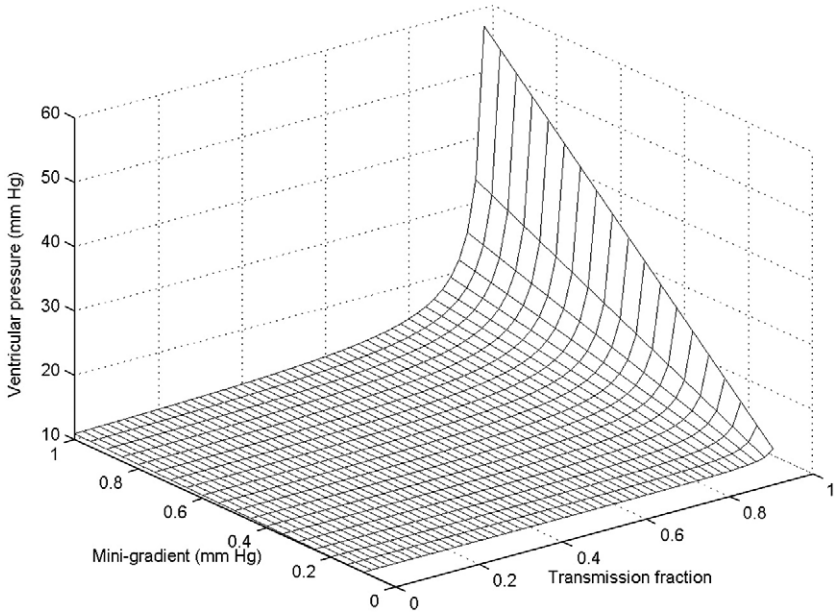

Fig. 3. Ventricular pressure as a function of the transmantle pressure mini-gradient and the degree of pressure transmission from ventricle to brain surface. Ventricular pressure increases linearly with the required mini-gradient and non-linearly with the degree of pressure transmission. The region of moderate to higher mini-gradients and high degree of pressure transmission corresponds to the elevated ventricular pressure of tension hydrocephalus.

obstruction by 1 mm Hg instead of the normal difference of 0.06 mm Hg. Suppose, too, that the elastic characteristics of his brain are such that 95% of any change in ventricular pressure is transmitted to the periphery. Intraventricular pressure must increase to 29 mm Hg and subarachnoid pressure, to 28 mm Hg. The patient would have tension hydrocephalus with a transmantle gradient of only 1 mm Hg. Second, suppose another individual develops a smaller obstruction that requires ventricular pressure to exceed the subarachnoid pressure by only 0.5 mm Hg and has a brain with an efficiency of transfer of only 50%. In this case intraventricular pressure increases only to 11 mm Hg, and the pressure in the subarachnoid space increases to 10.5 mm Hg. The patient has normal pressure hydrocephalus with a transmantle gradient of 0.5 mm Hg.

As a result of the non-linear relationship between ventricular pressure and the efficiency of pressure transmission, the difference in magnitude between the ventricular pressure and the transmantle pressure gradient becomes very striking when the efficiency of pressure transmission is high. The relationship between ventricular pressure and the transmantle pressure gradient is analogous to the relationship between pre-tax income and after-tax income if the fractional transmission of pressure is thought of as the tax rate. Just as obtaining a given after-tax income requires a much higher pre-tax income if the tax rate is prohibitive, so ventricular pressure must become very high if the transmission of ventricular pressure to the periphery is very efficient. This is illustrated for two cases with the same small transmantle gradient but different efficiencies of pressure transmission in Fig. 4. For the same transmantle pressure gradient ventricular pressure must be much higher if the efficiency of pressure transmission is 98% than if it is 80%.

4. CSF pressure and volume in the cranial subarachnoid space

We have assumed that the transmission of increments in ventricular pressure to the outer surface of the brain is reflected in a corresponding increase in CSF pressure in the subarachnoid space over the cerebral hemispheres distal to the obstruction to CSF flow. This assumption has empirical support. While the sulci over the cerebral convexities may be compressed in hydrocephalus, there have been no reports of any significant differences between the CSF pressure within the subarachnoid space and either the pressure in the subdural space just outside it, or the tissue pressure on the outer surface of the brain abutting the subarachnoid space on its inner pial surface.

To understand why pressure in the compressed cerebral subarachnoid space is equal to pressure in the adjacent subdural and subpial spaces, one must consider the transmitted forces acting on the subarachnoid space. An increment of intraventricular pressure is transmitted outward as radial compressive stress as soon as outward movement of the surface of the brain is constrained by the overlying skull, dura, and subarachnoid space. The forces acting on the subarachnoid space are depicted in Fig. 5. A force acting inward on the arachnoid, exerted by the skull and dura, is opposed by an equal and opposite force acting outward on the pia, exerted by the outer surface of the brain. These compressive forces on either side of the subarachnoid space must either collapse that space or be balanced by equal (or

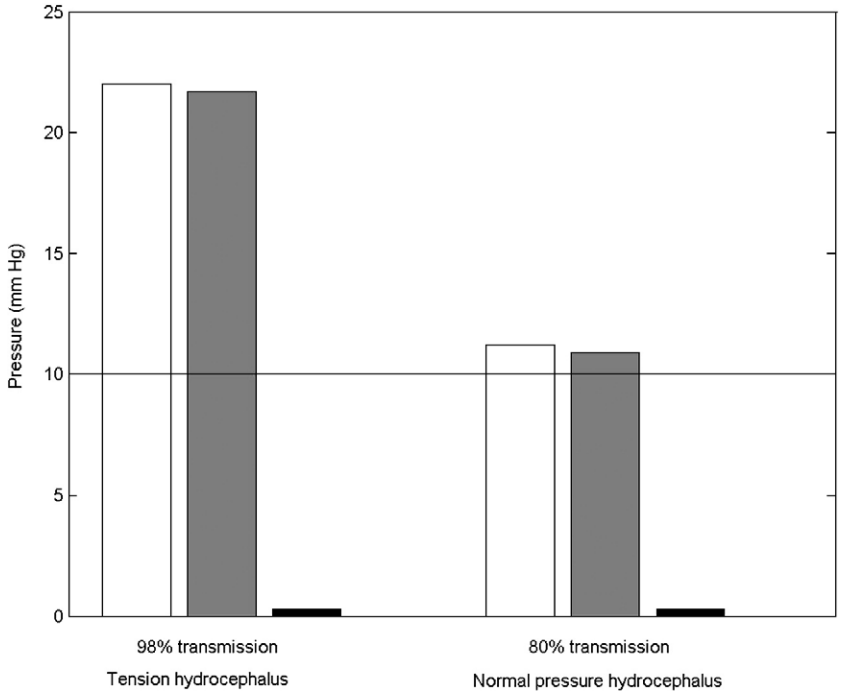

Fig. 4. Illustration of the importance of degree of pressure transmission in determining intracranial pressure in hydrocephalus. The group of three bars on the left represents a case with 98% transmission of changes in ventricular pressure to the surface. The group of three bars on the right represents a case with only 80% transmission. In both cases the required mini-gradient is 0.3 mm Hg. In each group the white bar is ventricular pressure, the gray bar is pressure in the cranial subarachnoid space, and the small dark bar is the difference between the white and the gray bars — i.e., the mini-gradient. A high degree of transmission produces tension hydrocephalus, while lower degrees of transmission cause normal pressure hydrocephalus. The horizontal line at a pressure of 10 mm Hg represents the assumed normal intraventricular pressure.

greater) pressure within the subarachnoid space itself. Although the delicate arachnoid trabeculae may be capable of bearing slight tension, allowing pressure in the subarachnoid space to exceed slightly the pressure outside it, there is no anatomic structure allowing resistance to compression to prevent collapse.

If the cranial subarachnoid space were a closed system, bounded by thin walls incapable of bearing tension, any increment in pressure exerted uniformly on the outside walls would be fully transmitted to the incompressible CSF without change in the volume of the cranial subarachnoid space. However, the cranial subarachnoid space is not closed. CSF can exit in two ways, and this possibility allows for reduction in volume of the subarachnoid space despite full transmission of the radial compressive stress to it. First, CSF can be absorbed into the dural venous sinuses. If the sinuses remain open, the CSF pressure will rise but the volume of the CSF space will progressively decrease with continued absorption. However, the sinuses may not remain open [28–31]. Their walls, although thicker than the more delicate pia-arachnoid, may collapse if the transmitted radial compressive stress sufficiently exceeds the blood pressure within the sinuses. Collapse of the sinuses would interfere with CSF absorption and cause CSF pressure to rise without further decrease in CSF volume. Second, CSF can cross the foramen magnum from the cranial subarachnoid space to the spinal subarachnoid space. The spinal dura, particularly in the lumbar region, is extensible. This compliance allows transfer of CSF from the cranial to the spinal subarachnoid space, decreasing the volume of the cranial subarachnoid space until the pressure needed to sustain the spinal dural stretch equals the transmitted radial compressive stress.

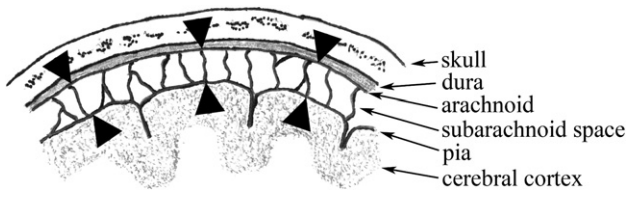

Fig. 5. Schematic drawing of the outer surface of the brain and its coverings. The arrowheads represent the radial compressive stress tending to collapse the subarachnoid space. Inward pointing arrows are the force exerted by the skull and the dura on the arachnoid. The outward pointing arrows are the equal and opposite forces exerted by the outer surface of the brain on the overlying pia.

There is also the possibility that radial compressive stress is transferred to the subarachnoid space in part through its effects on pressure within the pial and cortical veins. Compressive stress in the subdural space may narrow the terminal portions of the cortical veins as they enter the dural sinuses. This vascular narrowing on the venous side of the circulation, coupled with myogenic dilation of the small arteries and arterioles [32,33] alters the topographical distribution of resistance to blood flow, shifting it from the arterial side of

the circulation, where it is normally heavily concentrated in the small arteries and arterioles, towards the venous side. As a result of this redistribution of vascular resistance, pressure within the cortical veins rises significantly [34,35]. Bateman [36,37] has shown that the compliance of the convexity cortical veins is reduced in hydrocephalic patients and returns to normal after shunting. The reversible reduced compliance is consistent with increased cortical venous pressure. The cortical veins have thin, flexible walls which transmit their intraluminal pressure to the CSF of the subarachnoid space. This transmission may require only slight venous dilatation because of the limited compliance of the CSF space, which resides primarily in the spinal dura. Several investigators [38–40] have shown that at least 60% of an elevation in venous pressure is transmitted to the CSF space.

5. Determinants of intracranial pressure in hydrocephalus

In Section 3 we showed that the difference between hydrocephalus with increased intracranial pressure and hydrocephalus with normal pressure is determined by 1) the size of the transmantle pressure gradient needed to ensure CSF absorption; 2) the efficiency with which incremental pressure on the ventricular wall is transmitted to the surface of the brain; and 3) the effects of ventricular dilatation. We now examine the clinical situations that determine the values of these variables and thus the prevailing intracranial pressure in hydrocephalus.

The size of the transmantle pressure gradient is determined by the severity of the obstruction and by the availability of alternative pathways for CSF absorption. As alternative paths likely require time to develop, a sudden severe obstruction favors tension hydrocephalus, while a more gradually developing obstruction favors hydrocephalus with normal pressure throughout its course. Because ventricular pressure is linearly related to the transmantle pressure gradient, a sudden, extremely severe obstruction without alternative paths for CSF absorption may raise the required transmantle pressure gradient to a level beyond the small gradients that prevail in most patients and experimental animals with hydrocephalus. This will in turn require extremely high levels of ventricular pressure incompatible with survival.

The efficiency with which the increment of intraventricular pressure is transmitted to the surface of the brain is determined primarily by the poroelastic characteristics of the brain tissue and by ventricular size [26]. In the earliest stages of hydrocephalus — before significant interstitial fluid has been mobilized and absorbed into the bloodstream — the interstitial fluid can be treated as incompressible and the brain as a whole can be considered as a nearly incompressible elastic body. The only sources of compliance are egress of venous blood into the general circulation and displacement of CSF into the spinal subarachnoid space. This relative incompressibility favors effective conversion of any intraventricular increment of pressure into peripheral radial compressive stress. For example, in the dog Rekate et al. [41] found complete transmission of an increment of pressure in the cortical subarachnoid space to the lateral ventricles even after the two compartments were separated by obstructing the basal cisterns. Effective transmission is also favored by larger initial ventricular size (Fig. 2). Smaller ventricles means a thicker cortical mantle that is better able to absorb pressure against the ventricular wall and is thus less efficient in transmitting ventricular pressure to the periphery as radial compressive stress.

The process of ventricular expansion, which progresses as interstitial fluid is driven into brain capillaries, reduces the transmission of ventricular pressure to the periphery, lowering the peripheral compressive radial stress. In effect, the resorption of interstitial fluid becomes another source of brain compliance, albeit on a longer time scale. With reduced peripheral compressive stress the cortical veins decompress, and intracranial pressure decreases. Thus tension hydrocephalus — if survived — usually becomes normal pressure hydrocephalus. Although ventricular dilatation thus mitigates and reverses the general increase in intracranial pressure that may accompany acute hydrocephalus, it is still controversial as to whether it also compensates the defect in CSF absorption that gives rise to the transmantle pressure gradient itself. Such compensation will occur only to the extent that there is net transependymal flow of CSF and absorption of this CSF by brain capillaries and venules. If this occurs — perhaps through the ruptured or stretched ependyma — absorption increases as the ventricles enlarge and their surface area expands. This reduces and possibly eliminates the abnormal transmantle pressure gradient, so that the hydrocephalus may become truly arrested.

6. Implications for biomechanical characteristics of brain

According to the present theory, the current techniques for measuring resistance to CSF absorption by steady-state infusion [42,43] or perfusion [44] are not in fact measuring the resistance caused by obstruction of the CSF pathways that initiates hydrocephalus. The normal resistance to CSF absorption is not found within the ventricular system or the subarachnoid space but rather at the site of absorption, believed by most to be the arachnoid villi. Normal levels of resistance are on the order of 7 mm Hg per ml/min with 95% of values between 4.8 and 10.4 [45]. The increment in resistance to CSF flow in a patient with chronic communicating hydrocephalus is much smaller — on the order of 0.6 mm Hg per ml/min [24]. Such a small increment may be detectable in a population study with sufficient patients but is too small — given the above range of normal — to be useful in diagnosis of the individual patient. To the extent that CSF infusion tests are clinically useful they are likely detecting an additional secondary source of resistance. For example, infusion of CSF, in raising the CSF pressure in the subarachnoid space of hydrocephalic patients, may further

compress the dural sinuses, raising venous pressure within them and interfering with absorption.

Measurement of "brain compliance" by rapidly injecting a small bolus of artificial CSF and recording the change in CSF pressure thus produced [46] is commonly employed in patients with hydrocephalus. The test is useful in providing partial information about the elastic behavior of the intracranial contents. It is difficult, however, to relate such a test to the brain as a poroelastic structure. The characterization of a linear isotropic poroelastic system requires the specification of four independent constants. Three of these describe the change in volume either of the brain as a whole or of its fluid content in response to changes in either the external stress or the pressure of the fluid filling the pores. The clinical test of "brain compliance" would provide one of these three volumetric constants, termed the "unjacketed storage coefficient" [47], if the dura were rigid. Since the spinal dura is not rigidly constrained, the clinical test of "brain compliance" measures a combination of the elastic properties of the brain and of the spinal dura. Furthermore, because it tests the instantaneous pressure response to an injected volume, it provides information only about the "undrained" system. In the case of hydrocephalus this represents the very earliest stages before interstitial fluid has been mobilized and drained from the brain. However, it takes no account of this fluid movement, which takes place on a longer time scale, as a source of added brain compressibility. For this vital information knowledge of at least one constant characterizing the "drained" state is needed. These might be the change in fluid content per fractional change in brain volume (Biot–Willis coefficient), the change in external stress required to produce a unit change in fractional brain volume (bulk modulus), the Young's modulus, the Poisson ratio or the shear modulus — all determined under conditions of constant CSF pressure or after the disturbed pressure has returned to its initial value.

With the aid of an appropriate model relating stresses to strains one can infer at least approximate values for some of the mechanical constants of the brain. For example, it is possible to estimate the shear modulus of brain from the degree of ventricular expansion in hydrocephalus if one accepts the appropriateness of a linear poroelastic model in describing the slow compression of brain tissue as the ventricles enlarge. The poroelastic model of Levine [26] predicts that ventricular enlargement is approximately given by the formula $u = \frac{r_v \nabla p}{2G}\left(\frac{(1-2v)\left(\Gamma^3-1\right)}{2(1-2v)\Gamma^3+1+v}\right)$, where u is the increase in ventricular radius, ∇p is the transmantle pressure gradient, Γ is the ratio of brain radius to ventricular radius, r_v is the initial ventricular radius, v is the drained Poisson ratio, and G is the shear modulus. For typical values of Γ (3–4), the term enclosed within the large parentheses is approximately 0.5 for a wide range of values of v (0.00–0.45). The formula can thus be simplified to $u \cong \frac{r_v \nabla p}{4G}$. It is thus possible to estimate the shear modulus of the brain from knowledge of the initial ventricular radius, the pressure gradient between the ventricles and the subarachnoid space, and the degree of ventricular enlargement. For example, if the initial ventricular radius is 2 cm, and the ventricle expands in radius by 1 cm (increasing ventricular volume to approximately 340% of the original), the formula predicts that the required pressure gradient ∇p is approximately twice the shear modulus G. Since the present theory, supported by experimental measurements, suggests that ∇p is on the order of 25–100 Pa (0.18–0.75 mm Hg), one can predict that the shear modulus G is on the order of only 12–50 Pa. At first glance this value is surprisingly low given the data from the literature. Early investigators [48] had published values on the order of 3000 Pa. However, Miller and colleagues [49–51] have pointed out that the brain responds to deformation like a viscoelastic structure, in which the shear modulus varies with the rate at which the brain undergoes strain. In effect, the brain is stiffer the more rapidly it is deformed. Early investigators had used rapid strains that yield values of G that are inappropriately high for hydrocephalus, where the rate of deformation is extremely low. Taylor and Miller [51], on the basis of measurements at fast, medium and slow rates of deformation [49], have estimated that the shear modulus for extremely slow deformation is approximately 190 Pa. However, judging from Miller's published curves comparing calculated with actual stresses, even this relatively low value may be an overestimate. This may reflect the fact that his "slow" rate of compression was 7 mm/day, faster than all but the most acute cases of ventricular expansion in hydrocephalus.

Needless to say, the accuracy of such inferences is dependent upon the validity of the model that allows calculation of the material properties from measurements of strains and stresses. These models involve many untested assumptions of varying degrees of plausibility. For example, the assumption that material properties such as the poroelastic "constants" indeed remain constant during the course of a particular compression of brain tissue is likely false. They almost certainly change in value as the ventricles dilate, the periventricular tissue becomes disrupted and edematous, and the periphery of the brain loses interstitial fluid and is compressed. Thus the compliance of the brain, a reflection of its poroelastic characteristics, decreases with increasing ventricular size [52].

7. Limitations of the theory

The present theory postulates that an abnormal but very small gradient of static pressure across the cerebral mantle is sufficient to produce the ventricular dilatation of hydrocephalus. It is consistent with the physical laws governing the behavior of poroelastic bodies. It is also consistent with evolving evidence of the extreme compressibility of brain in response to prolonged application of small static stresses. It accounts for the numerous failures to detect large transmantle pressure gradients in hydrocephalic patients and experimental animals. However, the postulated mini-gradient has not yet been verified directly. The pressure transducers

employed to date have not been sufficiently sensitive, accurate and stable to distinguish an abnormal small gradient from a still smaller normal gradient, i.e., no abnormal static gradient at all.

A second and related limitation is that the theory has only indirect applicability to other views of the pathogenesis of hydrocephalus. The most prevalent of these alternative theories is that hydrocephalus is the result of abnormal pulsations of the brain [36,53–55]. With every heartbeat blood is delivered to the brain during systole and leaves during diastole. Because the intracranial volume is fixed by the rigid skull, the volume of blood that arrives must be matched at all times by an equal volume of blood, CSF or brain that leaves. Over an entire cardiac cycle the efflux of venous blood equals the influx of arterial blood, but the two processes are not synchronous. Arterial inflow exceeds venous outflow in systole and drops below venous outflow in diastole. To achieve the required moment-to-moment matching of entering and exiting volumes, approximately 1 ml of CSF crosses the foramen magnum into the more compliant spinal subarachnoid space during systole and returns during diastole [56]. If venting of the excess arterial inflow in systole is not adequate, the amplitude of the intracranial CSF pressure pulsation must increase. Inadequate venting may occur because pulsations are excessive, as in aortic insufficiency or in the primary arteriolar vasodilation of hypercapnia. Alternatively, the venting mechanism itself may be compromised. Venous outflow may be restricted, as in dural sinus thrombosis or congestive heart failure, or insufficient CSF may traverse either the aqueduct or the foramen magnum. The cause of insufficient CSF flow may be partial obstruction of the flow path from ventricle to spinal canal, or it may be reduced craniospinal compliance associated with increased intracranial pressure of any cause. With inadequate venting the resultant increased pulsatile CSF pressure subjects the ventricular walls to increased stress. Eventually this repetitive stress breaks down the periventricular tissue, resulting in ventricular expansion.

This form of pulsation theory of hydrocephalus [53,55] faces several difficulties. First, it is too broad, in that many of the conditions that increase pulsatility or reduce venting do not cause hydrocephalus. Hydrocephalus is not associated with aortic insufficiency or hypercapnia, which increase pulsatility. Nor is it associated with cervical spinal stenosis, cerebral edema, or pseudotumor cerebri, all of which reduce craniospinal compliance. Second, because it attributes ventricular expansion to irreversible tissue destruction, the pulsation theory cannot account for the prompt and marked reduction in volume of hydrocephalic ventricles occasionally seen after shunting. Third, the pulsation theory described above cannot explain why the periventricular tissue is more affected by hydrocephalus than the cerebral cortex, as both sites are adjacent to the pulsatile CSF. To meet the latter objection some pulsation theories posit a gradient of pulsations. Egnor et al. [54] postulate that reduced compliance in the subarachnoid space redistributes pulsations into the ventricular CSF, so that a transmantle gradient of pulsatile pressure amplitude exists between the ventricles, where the amplitude is high, and the subarachnoid space, where the amplitude is low. Bateman [36] postulates that narrowing and reduced compliance of cortical veins in hydrocephalus causes reduced pulsations peripherally in the brain, while pulsations generated in the periventricular region are excessive because of arteriolar dilatation and normal venous compliance in the territory of the deep venous drainage. It is to these forms of pulsation theory — those postulating gradients of pulsation amplitude across the cerebral mantle — that our theory has relevance. The same physical principles that demand instantaneous transmission of changes in static pressure from the ventricles to the outer surface of the brain apply to pulsatile pressures as well. There can thus be no large gradients of pulsatile pressure amplitude across the brain — only the mini-gradients discussed above. In support of this view Penn et al. [17] found no detectable differences in the amplitudes of pressure pulsations in the ventricles, cerebral parenchyma, or cerebral subarachnoid space of dogs with kaolin induced hydrocephalus. Stephensen et al. [18] also found no detectable differences between pulse amplitudes in the lateral ventricle and the cranial subarachnoid space in patients with hydrocephalus.

A third limitation of the present theory is that although the postulated mini-gradient is the effective force enlarging the ventricles, it is not the effective force responsible for some of the other features of hydrocephalus. Enlargement of the skull in hydrocephalic infants or expansion of the brain in adults with wide craniectomy depends on the absolute level of intracranial pressure rather than on the small difference in pressure between ventricles and subarachnoid space. That is because the infant's skull can be considered a curved shell subjected to intracranial pressure on the inside, and to constant atmospheric (zero) pressure on the outside. The gradient, or pressure difference, in this case is the absolute level of intracranial pressure — more specifically, the cranial subarachnoid and subdural pressure. It is likely that headache, papilledema, and the occasional other cranial neuropathies seen in hydrocephalus are also related to the absolute intracranial pressure, as they occur much more frequently in patients with tension hydrocephalus than in patients with normal pressure hydrocephalus.

8. Conclusions

The present theory reconciles the view that hydrocephalus is the result of obstruction to the flow of CSF with clinical and theoretical observations that the gradient in pressure from ventricle to subarachnoid space is often too small to be detected. It does this by showing that the intracranial pressure — intraventricular and subarachnoid — that prevails in hydrocephalus may be far higher than the pressure gradient needed to insure that CSF absorption matches CSF production. It must be higher because the poroelastic properties of the brain require that any increment of ventricular pressure be reflected in compressive radial stress at the periphery with

variable degrees of efficiency. However, it is the small pressure gradient and not the elevated intracranial pressure that is needed for the ventricular dilatation that characterizes hydrocephalus. Without it the ventricles do not enlarge, even if intracranial pressure is very high, as in dural sinus thrombosis or pseudotumor cerebri [57].

It is instructive to attempt to answer the three questions about normal pressure hydrocephalus posed by Hakim et al. [25] thirty years ago in light of the present theory. These questions, which have long vexed investigators, including this author, can be now be answered in a straightforward manner:

1. *Assuming that a high intraventricular pressure is needed to trigger hydrocephalus, why do the ventricles enlarge?* High intraventricular pressure is not needed — only a small difference in pressure between ventricles and subarachnoid space that upsets the balance of hydrostatic and osmotic pressure across brain microvessels and initiates absorption of interstitial fluid. High pressure complicates the underlying pathophysiology only because of initially low brain compressibility.
2. *Why do the ventricles remain dilated once intracranial pressure normalizes?* The normalization of intracranial pressure that was high at the outset of hydrocephalus is the result of interstitial fluid absorption which can be viewed as a large new source of brain compressibility that reduces the transmission of ventricular pressure to the periphery. The ventricles will remain dilated as long as the small pressure gradient that produced the dilatation in the first place is still present. Alternatively, if CSF is absorbed by the parenchyma as a result of flow across the ventricular wall, the ventricles may remain dilated even without an abnormal pressure gradient, because at the present ventricular surface area CSF absorption matches CSF production.
3. *Why does the patient with normal CSF pressure continue to show impaired neurological function?* Normal intracranial pressure in hydrocephalus does not preclude a small gradient — often less than 0.5 mm Hg — between the ventricles and the subarachnoid space. It is this gradient that triggers fluid absorption, ventricular enlargement, and shear stresses on brain tissue. It is these shear stresses — located predominantly in the periventricular white matter — that damage brain tissue and produce symptoms.

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