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Commentary

Normal Pressure Hydrocephalus: New Concepts on Etiology and Diagnosis

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Normal pressure hydrocephalus (NPH) is remarkable for two reasons: 1) it is one of the few treatable causes of dementia, and 2) neuroradiologists are usually involved in making the diagnosis. Hakim and Adams (1) are generally credited with the initial description of NPH, although it may actually have been described under a different name earlier by McHugh (2). It consists of the clinical triad of gait disturbance, dementia, and incontinence in a patient who radiographically has communicating hydrocephalus, ie, ventricles dilated out of proportion to any sulcal enlargement (which distinguishes it from atrophy) (3).

Over the 35 years since it was first described, the definition of NPH has been expanded. Initially it was considered to be idiopathic (4, 5); at present, common usage includes any form of chronic, communicating hydrocephalus (6, 7), and even a few noncommunicating forms such as aqueductal stenosis (8). Because all these patients may present with a similar clinical triad, and they may all be treated with a ventriculoperitoneal (VP) shunt, this expansion of the definition is probably appropriate, although certain secondary features distinguish the idiopathic form from communicating hydrocephalus with known causes. For example, the idiopathic form of NPH tends to present in the elderly (9), whereas patients with chronic communicating hydrocephalus from prior subarachnoid hemorrhage, meningitis, neurosurgery, or head trauma tend to present at an earlier age. Also, response to shunting seems to be worse (30–50%) for patients with the idiopathic form than for patients with a known cause of communicating hydrocephalus (50–70%) (10–12). Depending on the specific diagnostic criteria used, one half of the cases of NPH are considered to be idiopathic and one half result from a known insult; thus, NPH probably represents the final common pathway for a number of different disease processes (13–15).

The symptom complex of NPH has been explained on the basis of both mechanical (16) and ischemic factors (17–21). It has been suggested that the ventricular enlargement leads to vascular stretching (22), and the decreased compliance (23) and high pulse pressure leads to local ''barotrauma'' (20) or ''tangential shear stress'' (16). It has been postulated that the purpose of the shunt is to add additional capacitance to the system (24), increasing perfusion (22), not to decrease the pressure (which is already normal).

The gait disturbance is a gait ''apraxia'' and represents a combination of motor deficits, failure of postural righting reflexes, abnormal smooth pursuit, and failed suppression of vestibuloocular reflexes (13, 25). The gait has been described as ''magnetic'' because of the wide stance and slow, small steps with reduced floor clearance (13, 26). There is increased tone and brisk tendon reflexes in the lower limbs, and absence of weakness or incoordination (26). Impaired input from the sensorimotor cortex, the superior frontal cortex, and the anterior cingulate gyrus to the reticular formation in the tegmentum of the brain stem may also contribute to the gait and stance disorder (26, 27). Since the fibers of the corticospinal tract that supply motor function to the legs pass closest to the lateral ventricles in the corona radiata, it is not surprising that the gait disturbance is usually the first symptom to appear and the first one to resolve following successful VP shunting (28).

Problems with urinary functions begin with feelings of urgency, and in the later stages, develop into frank disinhibition (13). This may initially be due to involvement of the sacral fibers of the corticospinal tract (29), and later may be a feature of the dementia (13).

The dementia is subcortical (30, 31) and is characterized by inertia, forgetfulness, and poor executive function (13). The lack of cortical features helps to distinguish the dementia of NPH clinically from that of Alzheimer's disease. A number of groups have noticed an increased incidence of subcortical, deep white matter hyperintensities on T2-weighted MR images (20, 32–34). That these represent small vessel ischemia is further substantiated by the finding of decreased cerebral blood flow (CBF) (35–43), which generally improves after shunting (38).

The acetazolamide challenge test, which normally increases CBF, fails to do so in NPH patients, particularly in the periventricular white matter (44). This lack of the usual vasomotor response to carbonic anhydrase inhibitors (or to inhaled CO_2) probably indicates that the arterioles are already maximally dilated as a result of local ischemia (40). After CSF diversion, CBF in white matter generally improves, as does the response to acetazolamide (40). In addition to shedding some light on the role of autoregulation on the pathogenesis of the dementia of NPH, the acetazolamide challenge test has also been used to select patients for shunting

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(40, 44, 45). In this setting, the patients that have the best response to VP shunting have preoperative CBF above 20 mL/100 g/min (40).

The etiology of idiopathic NPH has been considered by many over almost 4 decades; however, no single theory has gained widespread acceptance. Ventricular enlargement can occur when the transmantle pressure (5), ie, the difference in pressure between the ventricles and the subarachnoid space, is increased (46), even temporarily (16, 47–51). Decreased CSF resorption increases transmantle pressure (16). CSF resorption in NPH is definitely abnormal, as shown by the saline infusion test (52). While many consider that CSF resorption occurs at the level of the arachnoidal villi (microscopic) or arachnoid granulations (macroscopic), other authorities feel that a substantial amount of CSF resorption occurs at the brain parenchymal level, ie, the transcapillary or transvenular level (53–56). (This is the reason that patients with obstructive hydrocephalus can resorb at least some CSF [53].) The fact that histologic analysis of the leptomeninges in idiopathic NPH fails to show fibrosis suggests upstream obstruction (57, 58) and lends credence to the increased venous resistance theory.

The theory proposed by Bateman in this issue of the *AJNR* (page 1574) suggests that increased transvenular resistance in the territory of the superior sagittal sinus is the initiating event in NPH. Since this could lead to ventricular enlargement and decreased blood supply in the same territory, it is an enticing theory—it encompasses the two major abnormalities in NPH. Dr. Bateman goes on to propose a test for diagnosing NPH based on quantitative measurements of the inflowing carotid or basilar arteries and the outflowing superior sagittal or straight sinus. Specifically, he suggests that the net systolic pulse volume and the temporal difference in the arterial and venous peaks are diagnostic of NPH. I have several problems with his methodology, particularly the use of prospective cardiac gating (which fails to sample the end of the cardiac cycle) (59) and scaling of arterial flow (either carotid or basilar) to match venous outflow (either in the superior sagittal sinus or straight sinus). I am also concerned about the small number of patients, the lack of blinding, and the use of normal controls almost 20 years younger than the NPH group. Regardless, if the same results could be reproduced with retrospective cardiac gating, if all blood flowing in and out of the brain were measured, and if this new test were performed on a larger number of both shunt-responsive and non-shunt-responsive NPH patients, then perhaps Dr. Bateman may be proven correct.

Over the years, a number of diverse tests have been used to select symptomatic NPH patients for VP shunting. Some tests are performed by radiologists, and some by neurologists or neurosurgeons. Nuclear or CT cisternography shows ventricular reflux with slow cortical uptake (60). Although this test reveals disordered CSF resorption at the level of the arachnoid villi, it is insensitive to increased upstream resistance at the level of the veins. Thus, while cisternography may have a role in diagnosing known causes of communicating hydrocephalus, it is less useful for diagnosing idiopathic NPH. In addition, it cannot predict shunt response because the patients may already have developed atrophy (20). Thus, a positive cisternogram coupled to a nuclear or Xenon CT study that shows normal CBF is much more successful than cisternography alone in predicting which patients will respond positively to shunting (61).

Lumbar puncture and removal of 50 mL of CSF (''tap test'') has been used extensively (62–65), although some (66) have doubted its accuracy for predicting the outcome from shunting. Recently, a ventricular tap test has shown much greater sensitivity and specificity in selecting which patients will respond to shunting, not surprising given that the test comes closest to simulating the actual VP shunt (9). Pressure monitoring via an intracranial transducer should show normal mean baseline pressure (hence the name) with transient elevations of mean and pulse pressure known as ''plateau'' or ''B'' waves. B waves occurring during more than 50% of the monitoring period (47, 48, 67–69) are associated with a greater likelihood of successful response to shunting. B waves may also be the cause of ventricular enlargement (54). Unfortunately, B waves may not be present during the monitoring period, decreasing their sensitivity as a test to diagnose NPH. Saline infusion with pressure monitoring has been used to reveal decreased CSF resorptive capacity (51, 52). Obviously, such tests are invasive and run the risk of infection.

Fifteen years ago, a number of investigators noted an increased aqueductal CSF flow void on the MR images of patients with communicating hydrocephalus (33, 70–72). In patients with clinical NPH, the extent of the flow void on proton density–weighted, non-flow-compensated, conventional spin-echo images has been highly correlated with a favorable response to CSF diversion (73, 74). Subsequent attempts to evaluate the CSF flow void on fast spin-echo images have failed (75, 76) (as might be expected due to the rephasing effects of the multiple 180° pulses). More recently, the volume of CSF pulsating back and forth through the aqueduct during systole or diastole (the ''aqueductal CSF stroke volume'') has been measured using phase-contrast MR imaging (77). Increased flow has been shown to correlate with a favorable response to shunting (77–80). In one report of shunt-responsive NPH patients with elevated aqueductal CSF stroke volumes, the CSF flow void was increased in only 50% of the conventional proton density–weighted images that had been performed with flow compensation. Thus, the important finding was that of hyperdynamic CSF flow, not of a prominent flow void per se. Hyperdynamic CSF flow is thus an indirect, but easily measured, sign of normal CBF and shunt-responsive NPH.

Normal or reduced aqueductal CSF flow indicates that CBF is reduced, atrophy is present, and there is a decreased likelihood of shunt response.

In my institution, if the patient has symptoms of NPH, a routine MR scan using conventional (not fast) spin echo is performed. If a prominent aqueductal CSF flow void is present, the patient is considered for shunting. (We have not seen a false-positive result on flow-compensated proton density–weighted conventional spin-echo images.) If the CSF flow void is normal, the patient undergoes a quantitative MR phase-contrast CSF flow study and, if positive, is considered for shunting. In my experience it is exceedingly unusual for a patient with hyperdynamic CSF flow not to respond positively to shunting (77). Using this algorithm, we have performed 100 quantitative CSF flow studies each year for the last 8 years for institutions throughout southern California.

The hypothesis that NPH is primarily a disease of increased venous resistance is interesting, but one might now ask, ''What causes the previously normal venous resistance to become elevated in elderly patients?'' I believe one could make a case for deep white matter ischemia being the initiating event. It is well known that NPH patients have a higher incidence of periventricular hyperintensities, ie, small vessel ischemic changes, than age-matched control subjects (17–21, 32, 34). Furthermore, it is known that the damage is more diffuse than that seen on T2-weighted MR images because the magnetization transfer ratio is decreased (81) (indicating loss of myelin protein) and the apparent diffusion coefficient is increased (82) (indicating increased interstial edema) in patients with normal-appearing white matter. Because the white matter is ischemic, the arteries are already maximally dilated, explaining the loss of autoregulation and lack of response to acetazolamide.

When the arterioles occlude, the draining venules close as well. Whereas this maintains the inflow-outflow balance for blood, the CSF normally drained by these parenchymal veins begins to back up until a new pathway can be found. According to the Monroe-Kellie doctrine, such a process might be expected to cause a transient elevation of intracranial pressure, ie, B waves. Because CSF is made by the choroid plexus within the ventricles, occluded venous drainage will lead to a transient increase in intraventricular pressure, resulting in ventricular enlargement.

The VP shunt may be effective for a number of reasons. For one, it may take up a greater proportion of CSF, taking the pressure off the parenchymal absorption route at the point of production within the ventricles. For another, it provides additional capacitance. If the VP shunt modulates the pulse pressure, there will be decreased interstitial edema, decreased interstitial pressure, improved perfusion, and decreased ischemia. (This may be the reason that third ventriculostomy has been effective in some patients with NPH [83].) The fact that patients with idiopathic NPH respond less frequently and more transiently to shunting than patients with known causes of communicating hydrocephalus (84) may be because small vessel arteriosclerosis is a steadily progressive disease. At some point, the shunt is no longer able to make up for the lack of parenchymal CSF drainage. Patients with the most severe white matter disease (85), or those with the lowest CBF (41, 43), probably do not respond to shunting because irreversible atrophy has already occurred.

A better understanding of the pathophysiology of NPH will undoubtedly lead to better patient selection and treatment. Bateman's article gives us new insights into the possible etiology of this complicated disease. I hope this will stimulate larger studies comparing MR-based tests of vascular compliance and aqueductal CSF stroke volume to the more invasive tap tests and intracranial pressure monitoring to best determine which patients will respond positively to shunting for NPH.

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