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Idiopathic Normal Pressure Hydrocephalus: New Findings and Thoughts on Etiology

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PERSPECTIVES

The Editorial Board Welcomes New Members

Individuals appointed to the Editorial Board of a scientific journal have an important but at times poorly understood job. According to a survey performed by Dr. Robert Quencer, former Editor-in-Chief of the *American Journal of Neuroradiology (AJNR)*, a few years ago, Editorial Board members responded that[1]:

- Editors-in-Chief spend 50% of their professional time working for their journal; only 45% receive some salary for this activity.
- Over 90% of journals have "Senior" Editors but only 20% are paid.
- 80% of Editorial Board members are selected by the Editor-in-Chief, 20% because they occupy prominent positions in their societies; none are paid.
- 50% of journals have nonsociety members on their Editorial Boards.
- 70% of Editorial Board positions are time-limited.

How are members of Editorial Boards chosen? Senior or Associate Editors are generally selected by the Editor-in-Chief and are individuals with aspirations/potential to become chief editors. Performance as a manuscript reviewer, recognition in one's field, and academic productivity are all taken into consideration when selecting members for an Editorial Board. I consider the Editorial Board of *AJNR* to be a working one and not an honorific one. Thus, all members are asked to review more manuscripts than our other reviewers and write editorials, opinions, and commentaries. *AJNR* Editorial Board appointments are limited to 2 years, and reappointments are given to those individuals whose work is considered to be exceptional. The *AJNR* is proud to have as members of its Editorial Board a mixture of younger and established investigators. Researchers as well as clinicians help us maintain balanced content. Not all members of the Editorial Board are American Society of Neuroradiology members.

How "American" is our editorial board? Out of 60 members, 10 reside outside of the United States. International members are critical to our mission as the pre-eminent journal in neuroimaging. They provide geographically diverse perspectives, and because they are generally "well-connected" individuals, they contribute to our impact factor by increasing our international visibility. They represent *AJNR* in distant meetings, provide cultural diversity, and enhance global communications. International advisory boards and peer reviewers are thought to increase international submissions.[2] In the future, I hope to increase the number of international members on our Editorial Board.

The benefits of being a member of an Editorial Board are many. Prestige, a sense of accomplishment, recognition by promotions committees, contributions to science, and being able to read articles before they are published are a few of them. The members of the Editorial Board also guide our authors in improving their manuscripts. Members of the Editorial Board of *AJNR* meet at least once a year, while Senior Editors and the Editor-in-Chief have monthly telephone conferences. This promotes solidarity and a feeling of "family" among us all.

This issue debuts a new Editorial Board. New members have been chosen from reviewers with the highest number and quality of manuscript reviews during the last 2 years. I look forward to working with them and welcome any suggestions. I also take this opportunity to thank those individuals who have finished their terms and sincerely hope that they will continue contributing to the *AJNR*.

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EDITORIAL

Idiopathic Normal Pressure Hydrocephalus: New Findings and Thoughts on Etiology

Having been interested in normal pressure hydrocephalus (NPH) for a quarter of a century, I am gratified to see 2 articles on this topic in this issue of the *American Journal of Neuroradiology* (*AJNR*).[1,2] Because of the original description of NPH by Adams et al[3] in 1965, many patients were shunted with only the symptom of dementia and, naturally, did not do well. Many questioned whether the disease even existed in the mid 1970s.[4,5] Fast forward 30 years to an editorial by neurosurgeon Robert Spetzler (Director of the Barrow Neurologic Institute),[6] who stated that NPH may account for as many as 10% of cases of dementia.

In the current issue of *AJNR*, Antonio Scollato et al (also a neurosurgeon) report on a series of patients diagnosed clinically with NPH who refused ventriculoperitoneal shunt surgery.[1] He performed MR phase-contrast CSF flow studies on them every 6 months for the next 2 years and discovered something very interesting: In some patients, the aqueductal CSF stroke volume (ACSV) increased on follow-up without any treatment. More than 10 years ago, I wrote an article indicating that if the ACSV was not elevated, the patients had less chance of responding to shunt surgery.[7] Specifically, the positive predictive value of shunt response for an ACSV >42 μL was 100%, whereas for stroke volumes less than 42 μL, it was 50%.

The way I interpret Scollato's findings is that the ventricles continue to enlarge after the patients become symptomatic with NPH. During the period before central atrophy sets in, the systolic expansion of the brain pushes against a larger drumhead, increasing the ACSV. Thus there will be a peak in the ACSV-versus-time curve when the ventricles reach their maximal expansion before atrophy (with decreased systolic

expansion of the brain). I had always assumed that the 50% of patients with ACSV <42 μL who responded to shunt surgery had "some" atrophy; now I realize that we might have studied them too early in the course of their disease and that their ACSVs might have subsequently increased, putting them into the "hyperdynamic CSF flow" mode.

As noted by Scollato, the number 42 μL is machine-dependent and could vary considerably from manufacturer to manufacturer and even from software level to software level. Thus, I recommend that anyone doing these CSF flow studies perform 10 studies on elderly patients without symptoms of NPH and without dilated ventricles to determine what is normal. I make a diagnosis of "hyperdynamic CSF flow" (which supports a diagnosis of shunt-responsive NPH) when the ACSV is twice normal.

Also in this issue of *AJNR*, there is an article by radiologist Grant Bateman, arguing that deep white matter ischemia (DWMI) is not a cause of NPH but rather due to decreased compliance of the superficial veins.[2] Using an elegant phase-contrast technique that measures arterial inflow, deep and superficial venous outflow, and ACSV, he shows that patients with cerebral blood flow higher than average have normal drainage from the straight sinus but 9% less drainage from the superior sagittal sinus compared with age-matched controls. I am not convinced that normal flow in the straight sinus proves that there is a lack of deep white matter ischemia, given the many articles that now document its increased prevalence in patients with NPH.[8] Although he does not question that deep white matter ischemia is present, he suggests that it is an epiphenomenon rather than the cause of NPH. Given the outward expansion of the brain against the inner table of the calvarium in communicating hydrocephalus, one might question whether the slightly decreased flow in the superior sagittal sinus is due to mild compression of the superior sagittal sinus and superficial cortical veins. Bateman notes the decreased compliance of the brain, based on decrease in the arteriovenous delay compared with healthy individuals. Could this also be an epiphenomenon rather than the cause of NPH? What causes some elderly patients to have decreased compliance in the first place?

Personally, I believe that DWMI is a cause of NPH but not the only cause.[9] I believe that NPH starts in infancy as benign external hydrocephalus also known as "benign macrocrania of infancy." This is a process that occurs in infants who present with an increasing percentile of head circumference compared with body length or weight. It has always been considered to be due to decreased resorption of CSF by "immature" arachnoidal granulations, which cannot keep up with the production of CSF. Because the sutures are still open at that age, the CSF accumulates in the slightly enlarged ventricles and in the frontal subarachnoid space and the head enlarges. We neuroradiologists caution against shunt surgery in these children because the arachnoidal granulations must mature at some point.

Actually, I am not sure they do. I think these individuals will always have decreased CSF resorption. Because saline infusion tests are not performed on babies, no one has really ever shown that CSF resorption improves. I think some of these babies will develop NPH 70 years later when they have a "second hit," namely, DWMI.[9] But let us go back and fill in some blanks.

With decreased CSF resorption via the arachnoidal villi and granulations, CSF needs a parallel path to exit the ventricles. I believe that this is the same path as is used by children with tectal gliomas, namely via the extracellular space of the brain, eventually punching through the pia into the subarachnoid space.[9] This can be modeled as a parallel electrical circuit diagram, corresponding to CSF outflow via the foramina of Lushka and Magendie and via the extracellular space of the brain.[9] Everything stays in balance (albeit with mild ventricular enlargement) until the onset of DWMI 70 years later when the symptoms of NPH appear.

DWMI is generally considered to be due to slow occlusion of the medium-sized vessels supplying the deep white matter, leading to the slow death of oligodendroglia. (This is not likely to be of sufficient magnitude to cause decreased blood flow in the straight sinus.) Histopathologically, DWMI appears as myelin pallor,[10] (ie, less lipid and more water, which is why it is bright on a T2-weighted images). Regarding the 70 year olds who had benign external hydrocephalus as infants, the CSF in the extracellular space, which was previously gliding over the myelin lipid, is now being attracted to the naked myelin protein. This increases resistance to CSF flow through the extracellular space, leading to back up of CSF, more ventricular enlargement, and symptoms of NPH.[9]

Is there any evidence for this theory? When more than 50 patients with clinical NPH and hyperdynamic CSF flow (ACSV 3–4 times normal) were compared with sex-matched controls, their intracranial volumes were significantly larger ($P < .003$ for men and $P < .002$ for women). The difference in volumes was only approximately 100 mL; however, it definitely suggested that the process began in infancy when the sutures could enlarge.[11] When apparent diffusion coefficient measurements were compared in patients with NPH and age-matched controls, they were significantly higher in the periventricular white matter for a given degree of DWMI, consistent with outwardly flowing CSF being dammed up by the DWMI.[9] I also have seen a number of cases in which the ventricles were enlarged 20 years before the patient developed symptoms of NPH, again suggesting that the process began much earlier.[11] How many times have we neuroradiologists seen enlarged ventricles without an obvious cause? We say "ventricles at the upper limits of normal" or "mild ventricular enlargement of uncertain etiology." These patients may develop NPH in the future, and as Scollato points out, there is only a limited temporal window to treat them.

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EDITORIAL

Intrathecal Gadolinium: Its Time Has Come?

The article in this month's *American Journal of Neuroradiology* by Albayram et al ("Gadolinium-Enhanced MR Cisternography to Evaluate Dural Leaks in Intracranial Hypotension Syndrome")[1] reviews the authors' experience with intrathecal gadolinium administration for the detection of CSF fistulas resulting in spontaneous intracranial hypotension (SIH). In their report, the authors reviewed 19 patients with clinical SIH in whom 0.5 mL of gadopentetate dimeglumine diluted with 4 mL of saline was instilled intrathecally 1 hour before fat-suppressed T1-weighted MR imaging. They found CSF fistulas in 17 of 19 patients; 14 of the fistulas were subsequently confirmed, but in 3, the exact site of the fistula was not identified due to the gross extent of leakage by the time the MR imaging was performed. Ten patients had a single fistula, whereas 4 patients had multiple fistulas (2 tears in 3 patients and multiple tears in 1 patient). Of importance, 4 patients, all with meningeal diverticula, showed only paravertebral leakage without prominent epidural leakage. Although the authors did not routinely compare intrathecal MR myelography with CT cisternography, 2 patients did have both studies, and 1 of these showed leakage along a nerve root on MR myelography that was not visible by using CT myelography. Clinically, no patients were found to have an untoward reaction, behavioral changes, or evidence of toxicity at 24 hours and at 6–12 months following the examination.

Di Chiro et al[2] first used intrathecal gadolinium to detect intracranial CSF fistulas in Beagle dogs (Beagles apparently occasionally have spontaneous CSF rhinorrhea). Using gadolinium MR cisternography, they identified fistulas in 2 dogs that had been previously found to have CSF rhinorrhea by radioisotope cisternography. In 1999, Jinkins et al[3] administered cisternal gadolinium to rabbits, showing no behavioral effects, good cisternal contrast, but "gradual diffusion of the gadolinium into the cranial parenchyma . . . on the delayed MR studies (45 minutes–6 hours), as revealed by progressive generalized enhancement of the brain." Zeng et al,[4] from the same group, first piloted the technique in humans, showing excellent opacification and no gross behavioral changes following the instillation of 0.2 mL, 0.5 mL, or 1 mL of gadopentetate dimeglumine (500 mmol/L) diluted in 5 mL of CSF. Although long-term safety studies have yet to be performed, histologic studies in animals have shown no changes concerning acute toxicity of intrathecal gadolinium, and a recent international registry study of 95 humans reported no significant toxicity of 0.5–1 mL of intrathecally administered gadopentetate dimegulmine.[5] Aydin et al[6] reported that gadolinium cisternography demonstrated leaks in 2 patients with negative findings on CT cisternography, and Tali et al[7] used gadolinium cisternography to determine the communication between the CSF pathways and intracranial arachnoid cysts. Although the spatial resolution of MR imaging is typically less than that achieved by using CT myelography, the lack of ionizing radiation and better contrast resolution are enticing factors that make MR imaging a viable alternative to CT, especially in children and in those in whom subtle or slow leaks are suspected.[8]

I have personally used gadolinium cisternography in several patients with SIH who had difficult-to-detect spinal fistulas. After obtaining informed consent from the patients, I diluted 0.5 mL of gadopentetate dimegulmine with 5 mL of iohexol (Omnipaque 180; GE Healthcare, Piscataway, NJ) and slowly injected this mixture intrathecally during a 3-minute period. The patients tolerated this procedure well and had no immediate or subacute side effects, and the technique allowed me to study the patients first with CT myelography, followed by MR myelography. Radioisotopes could also be administered at the same time by using a single spinal puncture.

Obviously gadolinium cisternography brings up concerns regarding the safety of the intrathecal use of gadolinium-based contrast agents. The intrathecal use of gadolinium is not currently FDA-approved. The off-label use of these compounds should be considered carefully and used only in patients with normal renal function and CSF clearance in whom currently accepted techniques for detecting CSF dynamics or leaks are either unrevealing or associated with unacceptable potential consequences or risks. Central nervous system (CNS) toxicity following the intravenous use of gadolinium in a patient with renal failure has been reported.[9] In addition, Morris and Miller[10] reported that the increased signal intensity in the subarachnoid space detected on fluid-attenuated inversion recovery imaging of the brain in patients following previous intravenous gadolinium injections is secondary to contrast agent crossing the intact blood-brain barrier in both healthy patients as well as those with renal failure. There are, no doubt, differences in the CSF clearance among the various compounds as well among patients with various renal clearances, ages, and underlying CNS disorders. The direct enhancement of brain as observed in rabbits by Jinkins[3] (see above) is also a concern that the brain is at risk for toxicity if CSF clearance is impaired or an improper dose is administered. These questions must obviously be addressed before general use of these agents intrathecally.

All that said, gadolinium MR myelography and cisternography may potentially better evaluate obstruction of the sub-