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Normal Pressure Hydrocephalus and Deep White Matter Ischemia: Which Is the Chicken, and Which Is the Egg?

I was excited when I first read the article ''^{1}H-CSI of Normal Pressure Hydrocephalus'' by Kizu et al (page 1659), which is presented in this issue of the *AJNR*. The authors describe finding spectroscopic evidence of intraventricular lactate only in patients with normal pressure hydrocephalus (NPH) and not in other patients with varying types of dementia or control patients. My excitement was based on my understanding that deep white matter ischemia may be one of the causative factors in the idiopathic form of NPH (ie, when there is no evidence of the usual causes of chronic communicating hydrocephalus, subarachnoid hemorrhage, and meningitis).

Actually, histologic evidence linking NPH and deep white matter ischemia was presented nearly 25 years ago (1), a decade after NPH was first described. Beginning more than 10 years ago, a number of us working in the field of MR imaging described a significantly higher incidence of deep white matter ischemia in patients with NPH than in age-matched control patients (2). Brain perfusion studies during the last decade have revealed decreased regional cerebral blood flow (CBF) in the periventricular region in patients with NPH. The decreased blood flow subsequently improved after shunt surgery. It has also been shown that although, in healthy patients, regional CBF increases in response to Diamox (ie, the acetazolamide challenge test), in patients with NPH, it does not. This finding implies that a state of ischemia already exists with maximally dilated arterioles, which cannot respond further to the challenge of a carbonic anhydrase inhibitor. Thus, this finding of intraventricular lactate in patients with NPH further supports the association of deep white matter ischemia and NPH. With this association in mind, the finding of intraventricular lactate in patients with NPH is not unexpected.

So, why do I think deep white matter ischemia contributes to the cause of idiopathic NPH? First, consider the normal movement of water in the brain. Water molecules leave the arterioles and upstream capillaries, enter the interstitial space of the brain, and then reenter the vascular system via the downstream capillaries and venules under a combined pressure and osmotic gradient. Excess water (eg, vasogenic edema from breakdown of the blood-brain barrier), flows centripetally, passing through the ependyma, to be absorbed by the ventricles. With increased intraventricular pressure, cerebrospinal fluid (CSF) is forced through the ependyma, forming interstitial edema. The bulk flow of water is reversed and becomes centrifugal, with some being absorbed via the transcapillary or transvenular parenchymal route and some passing peripherally through the extracellular space of the brain into the subarachnoid space to be absorbed by the arachnoidal villi and granulations.

Ventricular enlargement occurs when the transmantle pressure (ie, the difference in pressure between the ventricles and the subarachnoid space) is increased. Decreased CSF resorption increases the transmantle pressure. CSF resorption in cases of NPH is definitely abnormal, as shown by means of the saline infusion test. That histologic analysis of the leptomeninges fails to show fibrosis in cases of idiopathic NPH suggests that the cause of decreased resorption is not meningitis. No evidence of hemosiderin suggests that no previous subarachnoid hemorrhage has occurred. If no evidence of previous meningitis or subarachnoid hemorrhage exists, then what is the cause of the decreased CSF resorption?

I propose that patients with NPH have always had decreased CSF resorption, but this resorption has never been sufficient to cause symptomatic communicating hydrocephalus. Perhaps these patients are the children with benign external hydrocephalus (due to immature arachnoidal granulations) who improve but never achieve full resorptive capacity. Perhaps they are among those in whom an increased head circumference was never documented when they were children 60 years ago, but who also have never had 100% resorptive capacity. We have all seen the MR studies of asymptomatic patients with incidentally noted ventricles that are ''at the upper limits of normal'' or ''slightly enlarged,'' without any history suggestive of atrophy or hydrocephalus. Regardless, a precarious balance between CSF production and resorption may have existed in these patients

for decades. I think that with advancing age, deep white matter ischemia may push them over the edge, upsetting this balance. With the obliteration of deep white matter arterioles due to arteriosclerosis, the draining veins and capillaries would also be expected to partially close down as regional CBF decreases (3). Because this closing also decreases a pathway for CSF resorption, CSF accumulates within the ventricles, leading to further ventricular enlargement and, eventually, to the symptoms of NPH. Although Kizu et al suggest that ventricular enlargement increases the interstitial pressure in the periventricular region, leading to deep white matter ischemia, I think it is the other way around. Increased venous resistance from deep white matter ischemia leads to further ventricular enlargement and symptoms. Regardless of which event is the ''chicken'' and which is the ''egg,'' a vicious cycle of increasing ventricular enlargement and deep white matter ischemia occurs, which might well lead to NPH.

I had hoped that the article by Kizu et al might have strengthened the case for deep white matter ischemia as an etiologic factor in cases of NPH. This might have been the case if their control patients had been elderly, with deep white matter ischemia but without evidence of NPH. Unfortunately, they were much younger. Obviously, a much stronger case for the assertion that intraventricular lactate is a specific marker of NPH would have been made had the authors used age-matched control subjects, presumably with some evidence of deep white matter ischemia on MR images. As it is, I am left thinking that any elderly patient with deep white matter ischemia might have elevated intraventricular lactate levels, a finding that might have been shown had the authors chosen appropriately age-matched control subjects. For that matter, lactate normally present in the intraventricular CSF, and because its concentration is 2 mmol, it should be visible at spectroscopy (4). Therefore, instead of asking why lactate was seen in the patients with NPH, one might well ask why lactate was *not* seen in the control patients and in the other patients with dementia. Perhaps this finding was just a matter of degree, and the authors' technique is less sensitive to the presence of lactate compared with that of other investigators. If this is the case, then perhaps the mere finding of intraventricular lactate should not be a sign of NPH, but rather, a specific minimum concentration might be the sign.

I have other concerns regarding the spectroscopic findings presented by Kizu et al. I would have expected the *N*-acetylaspartate:choline ratio to be lower in the patients with NPH and in the other patients with dementia than in the much younger control patients. It was not. If one accepts the authors' assumption that creatine levels should remain constant, then the *N*-acetylaspartate levels were actually higher in the patients with NPH and in the other patients with dementia than in the younger control patients; this finding is contrary to conventional wisdom (4).

I was also surprised that the condition of the two patients who underwent shunt surgery for presumed NPH either stayed the same or worsened clinically. This finding raises the question of whether they ever had NPH. Although the selection criteria used seem reasonable, the purpose of any diagnostic study is to identify patients who are likely to respond to a particular therapeutic intervention (eg, ventriculoperitoneal shunt surgery for NPH). Thus, studies such as this that purport to have revealed a new, specific diagnostic sign really should be based on therapeutic response rather than preoperative presumptive diagnosis. In this context, if the patients who ultimately responded to shunt surgery had elevated intraventricular lactate levels compared with levels in age-matched control patients, the finding would have been much more cogent.

As a final (and some might say gratuitous) comment, I would like to address the authors' summary dismissal of hyperdynamic CSF flow as a sign of NPH. I agree with their comments that the CSF flow void sign described a decade ago (5) is no longer as sensitive an indicator of shunt-responsive NPH as it was when the work was performed in 1983 and 1984. In that early study, conventional spin-echo images without flow compensation were used. Later studies that disproved the finding used flow-compensated conventional spin-echo or fast spin-echo techniques (which are intrinsically flow-compensated because of the multiple pairs of 180° pulses). However, a closer review of the NPH literature would have revealed that several of us are now using phase-contrast flow measurements of CSF pulsating through the aqueduct; we have again shown that the finding of hyperdynamic CSF flow is highly correlated with not only the preoperative diagnosis of NPH but with *shunt-responsive* NPH as well (6).

In summary, Kizu et al have opened a new window of investigation into the diagnosis and etiologic factors of NPH. I hope that their article will inspire others to continue to investigate the link between deep white matter ischemia and NPH by using new tools, such as proton spectroscopy.

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References

1. Koto A, Rosenberg G, Zingesser LH, Horoupian D, Katzman R. **Syndrome of normal pressure hydrocephalus: possible relation to hypertensive and arteriosclerotic vasculopathy.** *J Neurol Neurosurg Psychiatry* 1977;40:7379
2. Bradley WG Jr, Whittemore AR, Watanabe AS, Davis SJ, Teresi LM, Homyak M. **Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus.** *AJNR Am J Neuroradiol* 1991;12:31–39

3. Bradley WG. **Normal pressure hydrocephalus: new concepts on etiology and diagnosis.** *AJNR Am J Neuroradiol* 2000;21: 1586–1590
4. Danielsen ER, Ross BD. ***MRS Diagnosis of Neurologic Diseases.*** Marcell Dekker, 1999
5. Bradley WG Jr, Whittemore AR, Kortman KE, et al.**Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal pressure hydrocephalus.** *Radiology* 1991;178:459–466
6. Bradley WG Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P. **Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging.** *Radiology* 1996;198:523529