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Commentary

Chronic Communicating Hydrocephalus and Periventricular White Matter Disease: A Debate with Regard to Cause and Effect

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For an increasing number of pathologic conditions, the in vivo information obtained by radiologic brain imaging is often more accurate than that obtained from postmortem examination of the brain. This is true for the intriguing and complex condition of "normal pressure" hydrocephalus (NPH). Patients with NPH often are helped dramatically by shunting, which can mean the difference between being in a wheelchair (or bedridden) and being ambulatory, with additional improvement, though usually less dramatic, in cognitive function and memory. Though clinicians are turning increasingly to the neuroradiologist to determine whether hydrocephalus is present, a set of definitive and consistent in vivo diagnostic markers remains elusive. It is for these reasons that innovative work in this field is of great interest to radiologists as well as to clinicians. However, to convince the clinical community of the usefulness of our findings, we must apply the same stringent criteria used in other scientific disciplines.

In this issue of the *AJNR*, Bradley et al. [1] attempt to establish a cause-and-effect relationship between white matter lesions and hydrocephalus. I would like to discuss three issues related to their article: the pathology of periventricular white matter lesions, the relationship of white matter disease to hydrocephalus, and the diagnosis of NPH.

Pathology of Periventricular White Matter Lesions

The wide prevalence of white matter lesions in the elderly (known for several years as periventricular lucencies on CT [2] and more recently as subcortical T2 hyperintensities or UBOs on MR [2, 3]) is now well known both to the radiologic and the general medical community. Bradley et al. [3] were among the first to identify these lesions on MR images. Several studies [2, 4, 5] with pathologic correlation have found that these lesions are due to demyelination, hyalinization of arterioles, and, rarely, infarction. Awad et al. [4] found that small areas of infarction were only "occasionally" present in their autopsy material. Kirkpatrick and Hayman [5] found only one deep white matter infarct in 12 brains with white matter lesions. Lotz et al. [6] found white matter infarcts in 7 of 17 brains showing antemortem CT evidence of white matter lucencies. In the study by Marshall et al. [7] of three brains with white matter lesions, one brain had multiple deep white matter infarcts, one had a small solitary infarct, and one had two deep infarcts. Thus, white matter infarction does occur, and it accounts for a certain number of periventricular hyperintensities. However, I think it is clinically unwarranted to consider all white matter lesions as infarcts. In fact, the evidence supports that most are not infarcts.

Is it necessary to distinguish between deep white matter infarction and the more commonly seen microvascular changes due to demyelination? On the one hand, patients with subcortical infarcts show deficits in cognition and memory, although these are usually less severe than those associated with cortical infarcts. On the other hand, patients with noninfarct microvascular disease do not show cognitive deficits [2]. On fine motor testing, they may show subtle deficits

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[8], and they may be at greater risk for falls [9]. Thus, a substantial difference exists structurally and functionally between (1) patients with deep white matter infarcts and (2) patients with periventricular microvascular disease uncomplicated by infarcts. Clinical management seldom is affected by our determination, and therefore we are not usually asked to make this distinction.

In order to make the distinction between infarcts and microvascular disease, proton-density and T1-weighted images can be helpful. The patches of demyelination due to microvascular disease tend to be poorly demarcated, and on proton-density images, they show higher signal intensity than CSF. Infarcts tend to be more sharply marginated, and on T1-weighted sequences, they show lower signal intensity than brain. The patches of microvascular disease rarely are visible on T1-weighted sequences.

In addition, single-photon emission CT (SPECT) perfusion scanning with I-123 iodoamphetamine or ^{99m}Tc-HMPAO [10, 11] may become a valuable differential diagnostic tool. SPECT studies have shown little in the way of deficits in association with microvascular disease, whereas true infarcts generally show perfusion deficits that are extensive and often much larger than might be expected for the size of the structural lesions. This, however, is a matter that needs to be proved.

Thus, I would discourage the blanket use of the diagnosis deep white matter infarcts when describing periventricular T2 hyperintensities, and I would encourage an attempt to make the distinction between microvascular disease and subcortical (deep white matter) infarcts or, if this is not possible, to use the less specific terms microvascular disease or hypertensive-type microvascular disease.

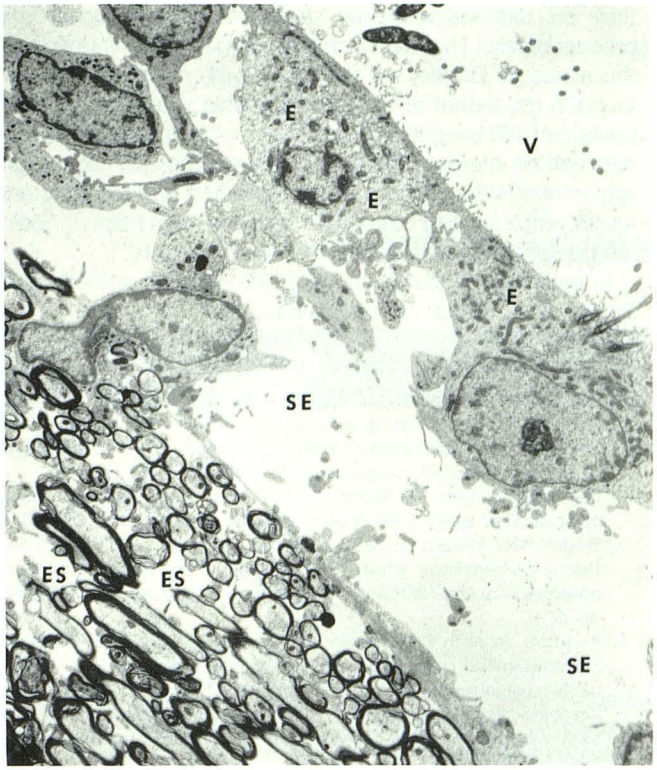

Fig. 1.—Chronic hydrocephalus induced by injection of kaolin into cisterna magna of a cat [16]. Semithin tissue section stained with toluidine blue shows intact ependymal lining (E). Ventricles (V) are enlarged markedly, and ependyma is separated from subependymal (SE) region, which is permeated by increased fluid content. Extracellular space (ES) also shows increased fluid (chronic edema). (Specimen compliments of G. Hochwald, NYU Medical Center.)

Relationship of Microvascular Disease to Normal-Pressure Hydrocephalus

The objective of Bradley et al. [1] was to determine if a statistical association exists between microvascular disease (which they choose to call deep white matter infarction) and NPH. This effort stems from previous reports in the neurologic literature dating as far back as 1943 [12] that have noted an association between hypertension and hydrocephalus [13, 14]. Bradley et al. found a statistically significant association between T2 hyperintensities and NPH. However, this association may or may not be one of cause and effect. In fact, periventricular changes in hydrocephalus may be the result of the hydrocephalus and not the cause. Light and electron microscopic studies [15, 16] of experimental hydrocephalus have shown detachment of the ependymal cells, rarefaction of subependymal tissues, and a marked increase in the subependymal extracellular space resulting in irreversible damage to the axons and myelin and gliosis (Fig. 1). These changes would be expected to appear as T2 hyperintensities on MR. Furthermore, reports [17–20], including our own [20], in the literature dating back to the 1960s on positron emission tomography (PET) and cerebral blood flow found that a reduction in blood flow, as well as in metabolism, is associated with hydrocephalus and that it improves after shunting procedures. Matthew et al. [19] reported that both cerebral blood flow and blood volume increased after lumbar puncture in patients with NPH. Patients with maximal increases in cerebral blood flow and cerebral blood volume after shunting showed the most consistent clinical improvement. This evidence suggests that the periventricular structural and functional changes may be the result rather than the cause of the NPH. Bradley et al. need to prove that the opposite is true before we can accept their hypothesis.

Diagnosis of Hydrocephalus

On the basis of their criteria for hydrocephalus (ventriculomegaly associated with increased CSF flow void), Bradley et al. [1] report that 83% of 72 consecutive patients with presumed deep white matter infarction also have hydrocephalus. This astounding result begs the question: How accurate are the criteria used to establish the diagnosis of hydrocephalus? The authors previously reported [21] that NPH is best distinguished from atrophy on the basis of a marked CSF flow void resulting from the to-and-fro motion of CSF through the aqueduct and contiguous third and fourth ventricles. Other investigators [22, 23], including our own, have been unable to replicate these results. In fact, Stollman et al. [23] found that the prevalence of CSF signal void was higher in their atrophy cases than in the hydrocephalus group. Only two of

their six patients who had shunts showed a signal void preoperatively. This sign was unchanged after shunting. In the series of Bradley et al. [1] as well, no difference was found in the extent of the CSF flow void when the pre- and postshunt MR images of four patients were compared. These data can be interpreted in only one way. The CSF signal void sign confirms the patency of the aqueduct and the third and fourth ventricles, but otherwise it has not been helpful. Again, the burden of proof remains with its proponents.

In summary, I advise caution. The innovative thinking of Bradley et al. should be commended.

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