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MR Imaging of Pseudotumor Cerebri

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Eleven obese young women with idiopathic pseudotumor cerebri were studied with high-field-strength (1.5 T) MR imaging to demonstrate increased water content in the brains of such patients. Heavily T2-weighted studies were obtained for 10 patients, and balanced (long TRs, short TEs, spin density, proton density) pulse sequences were obtained for four patients. We examined the studies of morphologically normal periventricular white matter and developed a white matter water index to determine if a slight increase in signal was present that could be ascribed to low levels of edema. Comparison was made to an age-matched control group. We also examined five patients with sodium MR imaging.

Two of the 11 patients had focal areas of increased signal in their periventricular white matter. Presumably, these are areas of increased edema above the background that could not be detected on the CT scan. The white matter water index for the normal controls was an average of 0.479 (±0.015), while that of the pseudotumor cerebri group was 0.520 (±0.016). This indicates an increase in the white matter water signal. We believe this represents a diffuse low level of edema. These findings are consistent with previous estimates of the increase in brain water in patients with idiopathic pseudotumor cerebri. The patients with focally abnormal proton studies demonstrated similar abnormalities on their sodium studies.

Pseudotumor cerebri or benign intracranial hypertension is a syndrome consisting of increased intracranial pressure with normal or small ventricles without evidence of obstruction. The presenting symptoms are usually headaches, various patterns of visual loss, and a CSF composition that is within normal limits [1, 2]. The role of radiology has been primarily to exclude other causes of increased intracranial pressure without providing a direct reliable sign for the diagnosis of this syndrome [3]. In the past, small or slitlike ventricles were considered a diagnostic finding in pseudotumor cerebri [4]. Later studies with pneumoencephalography and CT failed to support the specificity of the small ventricle as a diagnostic sign for pseudotumor [5–8].

The origin of pseudotumor cerebri remains obscure in many of its aspects. When patients with an identifiable cause of increased intracranial pressure such as high-flow vascular lesions, dural sinus thrombosis, and neurotoxic agents are excluded, the overwhelming majority of patients observed are obese young women. Many researchers believe that pseudotumor cerebri in this group develops from an intrinsic defect of water transport in the brain [9]. In fact, previous studies have shown increased brain-water content [10, 11]. We examined 11 obese young women with idiopathic pseudotumor cerebri using high-field-strength MR imaging to determine if abnormalities in brain-water content could be detected.

Subjects and Methods

Eleven women, ages 23–47, were studied. All of them presented with headaches, visual disturbances, and elevated opening pressure of lumbar puncture with no other clinical

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TABLE 1: Clinical Summary of Pseudotumor Cerebri Patients

Patient No.	Age	Weight (lbs)	CSF Opening Pressure	CSF Protein	EEG	Visual Loss
1	47	240	>550	40	Normal	Papilledema and field cuts
2	20	220	370	—	Normal	Papilledema
3	37	263	320	40	—	Papilledema
4	31	235	490	25	—	Papilledema
5	23	195	350	—	—	Papilledema
6	23	303	410	27	—	Papilledema
7	29	280	270	16	—	Mild papilledema
8	33	215	250	—	—	Papilledema
9	24	245	295	40	—	Papilledema and field cuts
10	31	230	410	26	Normal	Papilledema and field cuts
11	23	231	310	19	—	Papilledema and field cuts

evidence of neurologic disease. The clinical findings and laboratory values are summarized in Table 1. The duration of disease was not considered, since onset of symptoms is difficult to determine clinically and may not correspond with the onset of disease. In no case was there any evidence of dural sinus thrombosis or other conditions associated with brain edema, such as steroid withdrawal or thyroid disease. All the patients had normal CT scans. The MR scans were obtained at different times after the onset of the disease. Ten aged-matched controls with morphologically normal MR studies of the brain and normal CT scans provided the value of the white matter index in this series.

Ten of the 11 patients were studied with heavily T2-weighted proton MR imaging.* The pulse sequence used was a TE of 70 msec and a TR of 3960 msec. The control group was also studied with a TE of 70 msec and a TR of 3960 msec. This pulse sequence is particularly well-suited for quantitative evaluation of the water content of the brain. Refocusing gradient pulses were incorporated into the sequence to remove flow artifacts [12]. CSF pulsations and blood flow in most vessels was compensated for by this technique, thus improving the quantitative aspects of our measurements. Another important feature of this pulse sequence is the single-echo approach, which eliminates the artifacts found on multiecho sequences; namely, the potential of variation of slice thickness from one echo to another, the potential variation in image size due to eddy current effects, the variation of signal intensity due to the cumulative effect of RF inhomogeneity on subsequent echos, and the odd/even echo phenomena that affect moving fluids. Finally, a major advantage of this pulse sequence is the use of very long repetition times (more than 3.0 sec), a factor that has become recognized in our laboratory and in other investigators' laboratories as crucial for obtaining reliable, repeatable measurements of the T2 relaxation time. There are several explanations for the improved result with the unusually long repetition time, notably the direct elimination of the T1 effect, which is difficult to compensate for mathematically when a shorter TR is used. The multiexponential T1 relaxation is difficult to measure and varies unpredictably from region to region.

The evaluation of diffuse white matter edema was performed on the T2-weighted images by taking from an individual slice the ratio of the signal intensity arising from the periventricular white matter to the signal intensity within the ventricle. Multiple measurements of this ratio were obtained on each of three slices (Fig. 1) and the measurements were averaged and used as the white matter water index (Fig. 2). The same procedure was used in the control group. The actual intensity measurements are unique to our instrument and only represent relative values. Table 2 is a data set for a representative patient.

The size of the region of interest (ROI) cursor was as large as could be allowed to avoid averaging other structures (i.e., vessels, choroid plexus, gray matter). The cursor was placed in this fashion as well. The statistical significance of the results was tested with the Wilcoxon rank-sum test [13]. The proton signal arising from the brain on the heavily T2-weighted images is primarily related to the free water content of the brain tissue [14]. The decision was made to measure the signal in this fashion and not to use calculated T2 images because of a number of factors. CSF is relatively uniform in makeup from patient to patient and can effectively serve as water standard. Calculated T2 maps are frought with many potential inaccuracies. One of them is the assumption that the T1 relaxation is monoexponential while in reality it is multiexponential and cannot be characterized by only two or three points with different repetition times. The potential inherent variance has been noted to be as high as 8% [15–17], while the changes we are looking for have been calculated in the range of 4% [11].

Calculated T2 or T1 maps require, as a rule, a minimum of two data acquisition sequences with two different TRs. This methodology tends to introduce misregistration artifacts due to slight patient motion, which further decreases the accuracy of the technique. Also, calculated T2 and T1 maps are inevitably noisier images than the primary images. The use of a single-echo method with a very long TR (more than 3.0 sec) has in our hands produced the most reliable data for the detection of small differences in hydration because of reduced artifact and image noise. It is our belief that our system is at least as accurate as mapping and that it can therefore serve as an effective alternative.

Four patients and four controls were studied with a balanced pulse sequence (spin density). A TE of 36 msec and a TR of 3000 msec were used. A white matter water index was derived for these studies in the same manner as previously described.

Five patients were examined with the triple-echo sodium MR technique developed in this institution [18]. This method generates an image from the FID obtained at 0.6 msec after the 90° pulse, the second image is generated from an 18-msec echo, and a third image is generated from a 36-msec echo. The method uses a 3D planar projection reconstruction technique resulting in 18 images reconstructed on 128 × 128 × 128 matrix. The entire head is covered by this method. The first image obtained from the FID signal represents total sodium content of the brain while the images obtained from the second and third echoes represent the longer T2 components of the sodium. Measurement of signal intensity was not performed with the sodium studies, since no standard was included in the imaging protocol.

* Columbia-Philips prototype 1.5-T unit.

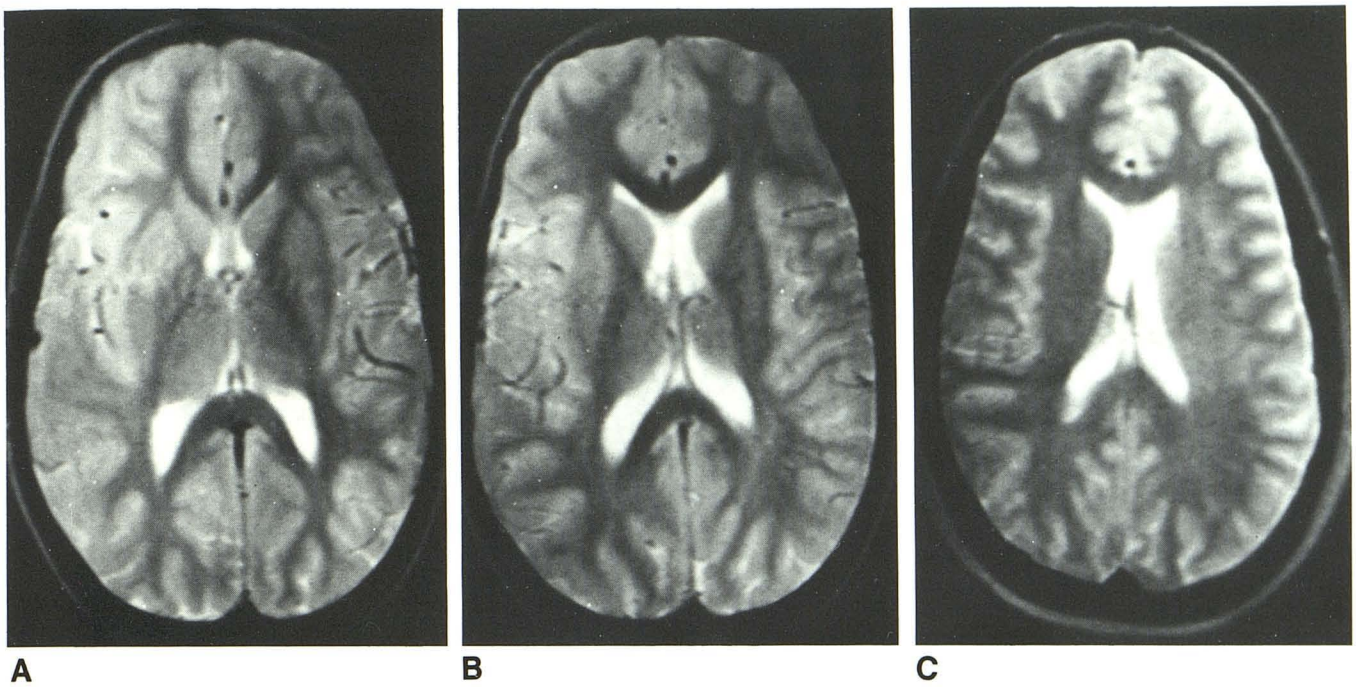

Fig. 1.—*A–C*, An example of the standard images from which the white matter water index was obtained (TE = 70, TR = 3960 msec).

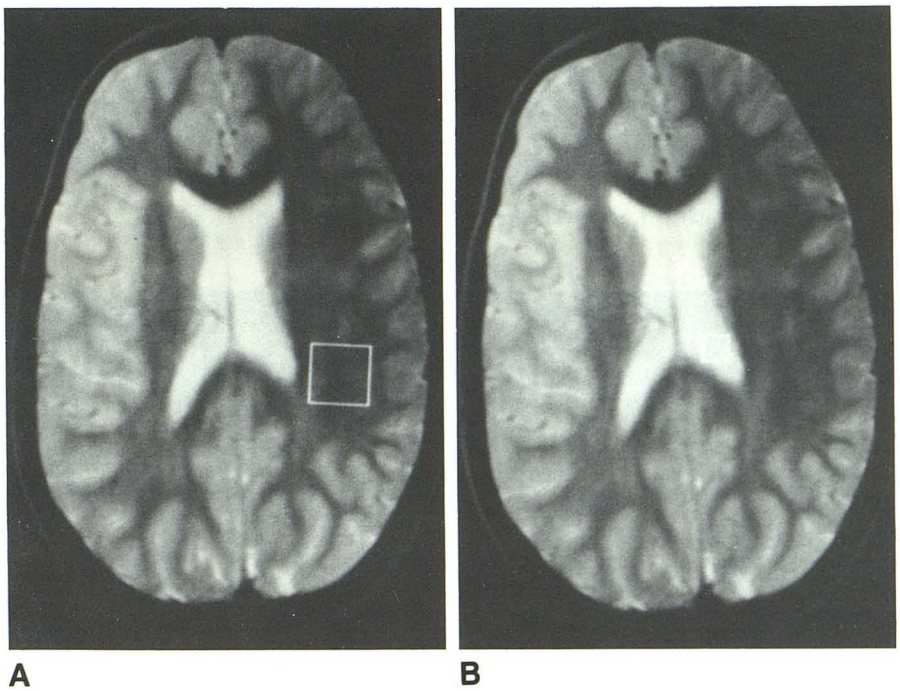

Fig. 2.—*A* and *B*, Representative typical positions of cursor and cursor size used in measuring white matter water index (TE = 70, TR = 3960).

Results

Of the 10 patients who underwent proton studies, eight had what appeared on the first inspection to be normal images (Fig. 3). Focal abnormalities were detected on the remaining two patients. The first of these two patients had multiple areas of increased signal intensity in the periventricular white matter (Fig. 4). This woman was the most severely ill in our group, with an opening pressure of greater than 550 mm of water. A second patient with focal lesions (patient 4) also showed increased signal intensity in the deep white matter (Fig. 5). This patient also suffered from severe recurrent

TABLE 2: Direct Measurements of ROI Relative Intensity Values Obtained on a Heavily T2-Weighted Study of a Single Representative Patient

	Image 1	Image 2	Image 3
White matter	120 121 123 125 (±2.16)	121 123 126 129 (3.50)	120 124 125 126 (±2.63)
CSF	232 234 236 238 (±2.58)	240 243 245 239 (±2.75)	236 237 240 242 (±2.74)
Ratio	.523	.516	.518
White matter water index = .519			

Note.—Standard deviations are given in parentheses.

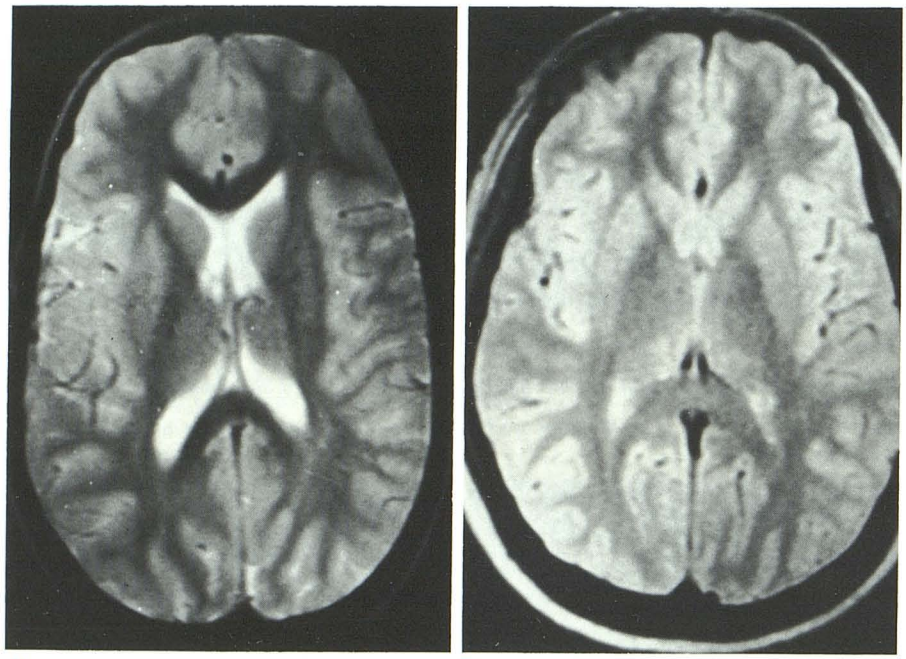

Fig. 3.—Examples of apparently normal images.
***A*, Heavily T2-weighted (TE = 70, TR = 3960).**
***B*, Balanced pulse sequence (TE = 36, TR = 3000).**

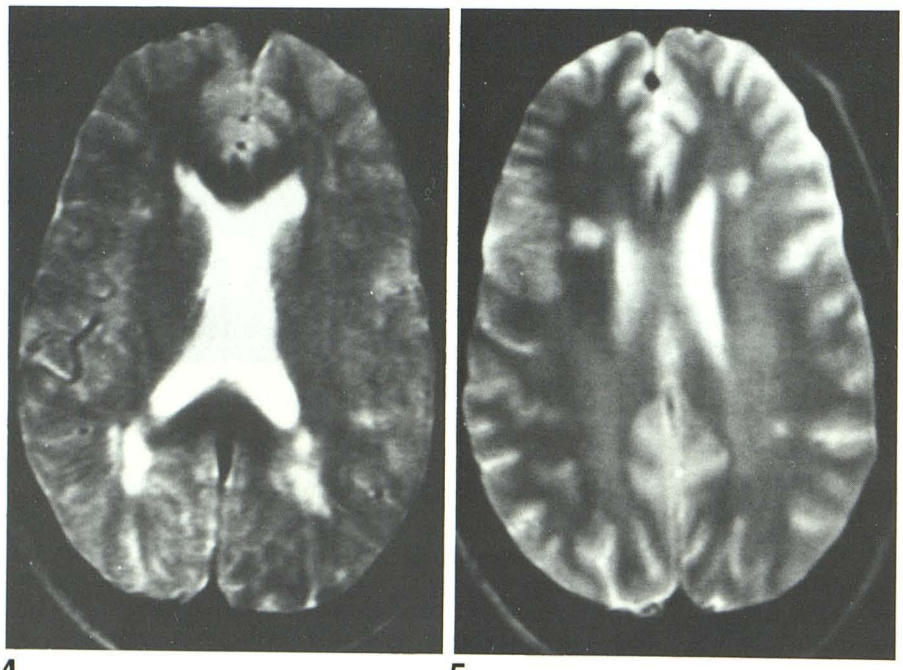

Fig. 4.—Representative MR image of patient 1 shows increased signal intensity in periventricular white matter (TE = 70, TR = 3960).

Fig. 5.—Representative MR image of patient 4 shows increased signal foci in deep white matter (TE = 70, TR = 3960).

pseudotumor cerebri and demonstrated a very high opening pressure (490 mm of water). Careful clinical examination and laboratory investigation revealed no other neurologic diseases: in particular, there was no evidence of demyelinating disease. Both patients had a normal CT scan before and after contrast administration. It appears, therefore, that these areas of increased signal intensity on the MR images may represent focal areas of edema that are below the level of sensitivity on the CT scan.

The white matter water index was measured in all 10 patients who had proton studies (Table 3). The pseudotumor group had a consistently higher white matter water index than the control group, with an average 0.4 increase in white matter in the patients with pseudotumor. The difference between the two groups was found to be significant by the Wilcoxon rank-sum test with a p value of less than .01. The generalized increase in brain water could not be readily distinguished on the MR images, which on superficial examination appeared normal. There was no significant difference in the white matter index of the morphologically normal white matter of the two abnormal studies and the morphologically normal patients.

The white matter water index of the patients studied with the balanced pulse sequence was also increased over that of the controls. The average of the pseudotumor group was .859. The average of the control group was .817 (Table 4).

Five patients had sodium MR studies. Three of the five patients had no discernible focal increase or decrease in their sodium signal. All of them had morphologically normal proton MR studies. The other two patients had focal areas of increased sodium signal. These were the two patients with abnormal proton studies, and the abnormalities correlated anatomically with the proton abnormalities (Fig. 6).

Discussion

The origin of pseudotumor cerebri is unknown. Biopsy studies by Sahs and Joynt [10] in 1956 showed both intra- and extracellular edema. Glial swelling was demonstrated as well as increased interstitial water. Based on the transit time of radiolabeled water, Raichle et al. [11] calculated an increase in the total brain water content from a normal of 79% to 83%. This percentage was deemed sufficient to account for the symptoms and signs seen in pseudotumor. CT scanning is apparently not sensitive enough to detect a slight increase in overall brain water content. The focal lesions present in two patients were also below the level of sensitivity on the CT scan.

TABLE 3: Ratio of White Matter/CSF Signal (White Matter Water Index): Heavily T2-Weighted Pulse Sequence

	Ratio	
	Patients	Age-Matched Controls
	.535	.456
	.519	.457
	.547	.498
	.540	.472
	.505	.480
	.507	.495
	.505	.476
	.510	.495
	.507	.484
	No proton study	
	.517	.481
Average	.520	.479
Standard deviation	.016	.015

TABLE 4: White Matter Water Index: Balanced Pulse Sequence

	Ratio	
	Patients	Age-Matched Controls
	.844	.808
	.853	.816
	.858	.821
	.881	.823
Average	.859	.817
Standard deviation	.016	.007

Current theories on the pathogenesis of pseudotumor cerebri center on a primary inability of the brain to transport water in a normal fashion. This defect results in a decreased absorption of CSF and a higher equilibrium pressure between the brain and the CSF space. The spectrum of severity of disease can be seen in our findings. Nine of our 11 patients had morphologically normal studies. We found that on careful measurement, however, the signal intensity of the white matter of all our patients was elevated as compared with normals. The measured values of the white matter water index (Table 2) had a high statistical significance (using the Wilcoxon rank-sum test). We felt that this statistical test was more appropriate than a t test because of the relatively low number of measurements [13].

A low level of brain edema would cause an increase in the T2 by lengthening the proton T2 signal slightly and by increasing the overall amount of signal present [19]. It is, however, possible that the increased signal in pseudotumor patients is not due to edema. A recent preliminary report of a study of patients with multiple sclerosis demonstrated slightly longer T2 signals in apparently normal regions of white matter [20]. This longer T2 was manifested by slightly increased signal intensity. The explanation was based on pathologic studies that demonstrated diffuse astrocytosis and changes in lipids. Our patients had no evidence of neurologic disease other than increased intracranial pressure. Although the percentage increase is not directly proportional to the amount of the edema (because of the lengthening of the T2), the increase in signal seen in our study approximates the increased water calculated in the previous studies [11]. It is important to note that the denominator of the ratio is the CSF, which we have presumed to be a free water standard. Therefore, at long TR pulse sequences CSF becomes a water standard. At short TR pulse sequences it no longer serves effectively as such a standard, since the predominant signal at short TR is not from free water but from other protons in other environments.

A smaller group of pseudotumor cerebri patients was studied with a balanced pulse sequence in an effort to measure

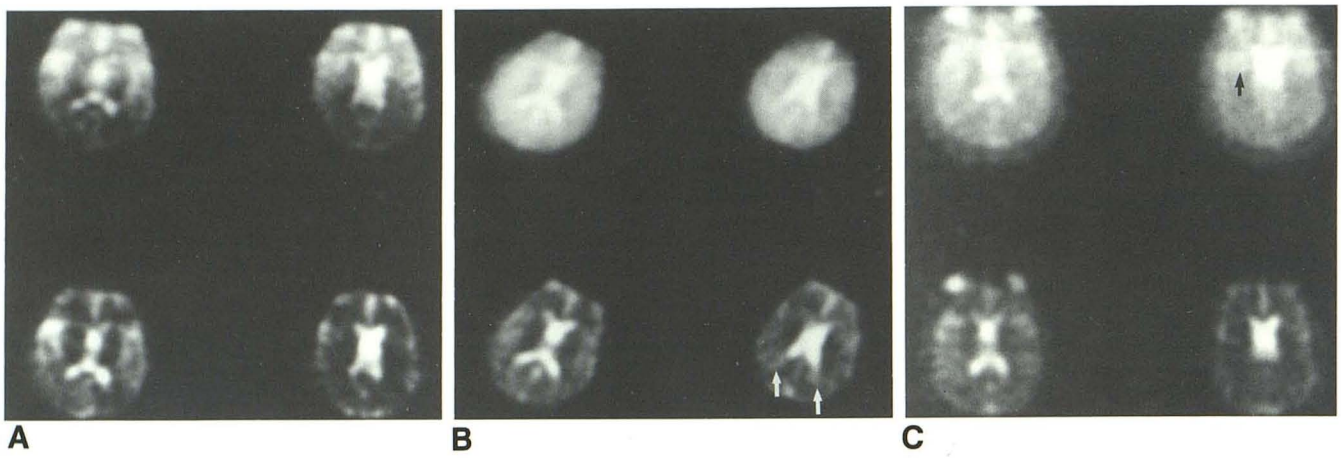

Fig. 6.—*A*, Normal sodium MR images. Upper two are FID images and bottom two are corresponding 18-msec images. *B*, Sodium study of patient 1 shows increased signal in periventricular white matter noted by *small arrows* (see Fig. 4). *C*, Sodium study of patient 4 shows increased signal in deep matter denoted by *small arrow* best seen on FID image (see Fig. 5).

total water signal and reduce the possible contributions of the other factors that could lengthen the T2 signal. Again we found an increase in the measured signal in the normal-appearing periventricular white matter. This finding supports the view that the increase in the signal is due to low-level edema. If the increase in signal were due to factors that only lengthen T2, then the signal intensity on the balanced studies would not be expected to increase. That the increase is of the same magnitude as the heavily T2-weighted studies is indicative that the extra water present is free water, also consistent with edema.

Two of our patients, probably not coincidentally the most severely affected, demonstrated focal areas of edema above that of the background. The increase in sodium signal is directly related to increase in edema fluid. Although there is a probable increase in intracellular sodium as well, the majority of the sodium ions exist in the extracellular space and the number of ions increase as the extracellular fluid (edema) increases. Sodium exists in at least three magnetic resonant relaxation states. Extracellular sodium is primarily in a long T2 state (25–50 msec), making its detection relatively accurate (18, 21, 22]. These lesions demonstrated increases in sodium signal. The increase in sodium is also consistent with previous reported findings [10].

Conclusions

We have examined 11 women with pseudotumor cerebri with a variation in the clinical state of their disease. We found consistently that signal from white matter free water is increased, representing a prolongation of the T2 relaxation time or an overall generalized increased level of water. That the signal intensity was also increased with balanced sequences is highly supportive of the view that the increased T2 signal is due to increased free water and not to prolongation of the T2 relaxation time. Increase in the white matter water index in the pseudotumor group as compared with the control group closely correlates with the increase in brain water content calculated by previously reported radioisotope studies. In the severe cases, we found changes in the morphology of the T2-weighted images and a corresponding focal increase in sodium content.

These findings are the first consistently demonstrable observations made in pseudotumor cerebri patients with an imaging technique. The increased white matter water index in this disease is most likely due to the remarkably high sensitivity of MR imaging to slight changes in water content [23]. We intend to follow these patients to determine whether, from changes in their MR studies, white matter signal can be used as a prognostic indicator in this disease.

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