

# Increased Brain Water Self-diffusion in Patients with Idiopathic Intracranial Hypertension

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**PURPOSE:** To investigate changes in brain water diffusion in patients with idiopathic intracranial hypertension. **METHODS:** A motion-compensated MR pulse sequence was used to create diffusion maps of the apparent diffusion coefficient (ADC) in 12 patients fulfilling conventional diagnostic criteria for idiopathic intracranial hypertension and in 12 healthy volunteers. **RESULTS:** A significantly larger ADC was found within subcortical white matter in the patient group (mean,  $1.16 \times 10^{-9} \text{ m}^2/\text{s}$ ) than in the control group (mean,  $0.75 \times 10^{-9} \text{ m}^2/\text{s}$ ), whereas no significant differences were found within cortical gray matter, the basal nuclei, the internal capsule, or the corpus callosum. Four of 7 patients with increased ADC in subcortical white matter also had increased ADC within gray matter. **CONCLUSION:** Measurement of diffusion coefficients in vivo demonstrated increased local water mobility within subcortical white matter in 7 patients with idiopathic intracranial hypertension that otherwise appeared normal on conventional MR imaging. Further studies are necessary to assess the clinical significance of these observations.

**Index terms:** Pseudotumor cerebri; Hypertension, intracranial; Brain, magnetic resonance

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Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure of unknown cause (1–5) and is also known as pseudotumor cerebri or benign intracranial hypertension. The symptoms and findings consist of headache, blurring of vision, transient visual obscurations, diplopia, papilloedema, no localizing neurologic signs except an occasional sixth nerve palsy, and a normal composition of the cerebrospinal fluid (CSF) (1, 3, 4). IIH is often a chronic disorder and can cause severe visual impairment or blindness (1, 3–5). The incidence of IIH is approximately 1 in 100 000 per year (2). The pathophysiology of IIH is unknown, although several mechanisms

have been suggested as possible explanations of the increased intracranial pressure: increased brain volume caused by increased brain water content (6–7), increased brain blood volume (8), increased rate of CSF formation (9), or a decreased CSF absorption at the site of the arachnoid villi (10–12).

With magnetic resonance (MR) imaging, it is feasible to measure the apparent diffusion coefficient (ADC) of brain water in vivo (13–19). The ADC measured in the brain reflects the local water mobility within the tissue, including the extracellular water fraction, the intracellular water fraction, and the blood volume. The contribution from perfusion is almost negligible because of the small vascular space. An earlier study of brain water diffusion in patients with IIH demonstrated increased ADC within periventricular white matter and in some patients also within gray matter (7). However, movement artifacts and pulsatile brain motion (20–22) were major sources of error in that study. To avoid these sources of error, we used a pulse sequence with first-order motion compensation. This MR sequence was used to study the ADC in the brain of patients with IIH and of age-matched healthy volunteers.

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TABLE 1: Patients with IIH included in the study and the calculated values of the ADCs ( $\times 10^{-9}$  m<sup>2</sup>/s) in different brain regions

Patient/ Age, y/Sex	Duration of Symptoms, mo	Mean ICP, mm Hg	R <sub>out</sub> , mm Hg/mL per min	Subcortical White Matter	Cortical Gray Matter	Nucleus Lentiformis	Capsula Interna	Corpus Callosum	Cerebrospinal Fluid	Motion Score
1/12/M	2	22	9.4	1.19	1.36	0.98	1.60	0.23	3.21	2
2/24/F	1	50	23.9	0.77	1.15	0.86	1.38	0.20	3.03	0
3/26/M	4	28	11.5	0.94	1.31	0.84	1.15	0.16	2.95	1
4/42/F	36	18	14.8	2.04	2.44	2.02	2.58	1.07	3.65	1
5/32/F	24	18	15.0	1.71	1.95	1.70	2.16	0.70	3.35	0
6/63/M	60	22	14.8	1.06	1.42	0.98	1.67	0.29	2.98	0
7/46/F	30	26	9.1	0.84	1.21	0.83	1.47	0.21	3.45	1
8/34/M	1	27	37.2	1.04	1.80	1.15	1.97	0.64	3.32	2
9/19/F	1	26	7.3	1.30	1.99	1.30	1.85	0.42	3.21	3
10/52/F	78	20	8.3	0.91	1.32	1.05	1.72	0.45	2.93	1
11/52/M	1	30	22.6	1.17	1.34	1.04	1.26	0.24	3.18	2
12/61/F	29	25	37.2	0.94	1.29	0.99	1.38	0.26	2.93	0
Mean (SD)	22.3 (25.9)	26.0 (8.5)	17.6 (10.6)	1.16 (0.37) <i>P</i> < .001*	1.55 (0.40) ns	1.15 (0.36) ns	1.68 (0.41) ns	0.41 (0.27) ns	3.18 (0.23) ns	

Note.—ICP indicates intracranial pressure (normal < 15 mm Hg); R<sub>out</sub>, resistance to CSF outflow (normal, < 9.10 mm Hg/mL per minute) (23); and ns, nonsignificant. \* *P* < .005 excluding patients with motion scores of 2 and 3.

## Materials and Methods

The study comprised 12 patients with IIH (7 women and 5 men). The age range was 12 to 63 years (mean  $\pm$  SD, 38.6  $\pm$  16.7 years) (Table 1). The diagnostic criteria used for IIH were: (a) increased mean intracranial pressure (more than 15 mm Hg); (b) symptoms and signs of increased intracranial pressure, but absence of any localizing signs except sixth nerve palsy; (c) no focal or diffuse disease on conventional MR; (d) normal or low protein concentration and normal cell count in the CSF; and (e) no clinical or neuroimaging suspicion of venous sinus thrombosis. Two of these patients were examined serially. Patient 2 was reexamined at 4 months and 8 months after the initial examination, and patient 9 was reexamined 4 months after the initial examination.

The mean intracranial pressure was monitored via a lumbar cannula, and the resistance to CSF outflow (R<sub>out</sub>) was measured by a lumbar infusion test (12, 23, 24). R<sub>out</sub> is the reciprocal value of conductance to CSF outflow and is less than 9.1 mm Hg/mL per minute in healthy volunteers (23).

Twelve healthy volunteers (5 women and 7 men) with no history of neurologic disease served as controls. The age range was 22 to 73 years (mean  $\pm$  SD, 37.4  $\pm$  18.0 years). The study was approved by the local ethics committee, and informed consent was obtained in all cases.

### MR Examination

The MR measurements were performed using a whole-body MR scanner, operating at a field strength of 1.5 T, with a maximum gradient strength of  $\pm$  10 mT/m. A standard circularly polarized head coil was used. To minimize head motion, a deflatable pillow was placed under the head. The brain was imaged in the axial plane using a double spin-echo 2500/15,90/1 (repetition time/echo time/excitations) sequence; section thickness was 5 mm with an intersection space of 1.8 mm, and the matrix size was 256  $\times$  256. Detailed descriptions of the theory behind MR measurements of water self-diffusion, as well as the actual pulse sequence used, have been reported previously (16) (Larsson H, Stubgaard M, Thomsen C, "In Vivo Measurement of Diffusion in CNS Using a Flow Compensated Spin Echo Sequence," abstract presented at the 9th Annual Meeting of the Society of Magnetic Resonance in Medicine, New York, August 1990). For the measurement of ADC, a spin-echo sequence was modified by the addition of bipolar gradients on both sides of the 180° refocusing radio frequency pulse (Fig 1). The diffusion-encoding gradients compensated for first-order motion; these gradients were in the same plane as the section-selective gradients making the pulse sequence sensitive to diffusion perpendicular to the section plane. Three different magnitudes of the diffusion-encoding gradients were used: 0.0, 7.1, and 10.0 mT/m, giving b values (14) of 0.00, 0.10 and 0.21  $\times$  10<sup>9</sup> s/m<sup>2</sup>, respectively. The time between the leading edges of the 27.5-millisecond-long diffusion-encoding gradients was 28.5 milliseconds, resulting in a

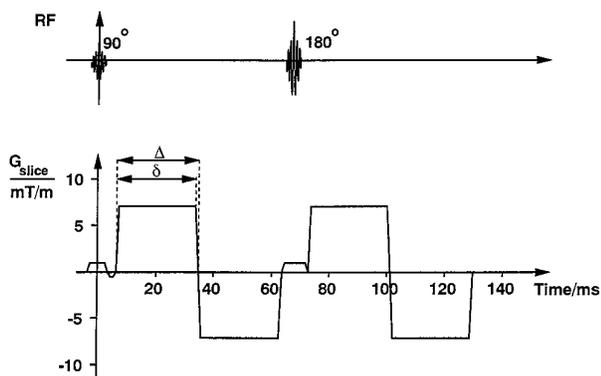


Fig 1. Timing schedule showing the diffusion pulse sequence compensated for first-order bulk motions.  $\delta$  indicates the duration and  $G$  the amplitude of the pulsed gradients;  $\Delta$  indicates the distance between the leading edges of the two pulsed gradients.

diffusion time of 19.3 milliseconds. These gradients were executed in a interleaved fashion. Electrocardiographic triggering was used to avoid influence of pulsatile brain motion. The sequence was triggered at every other R peak with a delay time of 0 millisecond; thus, repetition time ranged from approximately 1.6 to 2.4 seconds, giving an acquisition time of 25 to 40 minutes depending on the heart rate. Echo time was 134 milliseconds to obtain images directly after the R wave throughout the study. The number of excitations was 3. The section thickness was 8 mm, the field of view was 250 mm, and the matrix size was  $256 \times 256$ , giving a voxel size of  $1 \times 1 \times 8 \text{ mm}^3$ . The calculation of ADC is based on the formula:

$$\ln S(G) = \ln S(0) - 2 \times \gamma^2 \times G^2 \times \delta^2 \times (\Delta - \delta/3) \times D,$$

where  $D$  is the apparent self-diffusion coefficient;  $\delta$  is the duration and  $G$  the amplitude of the pulsed gradients;  $\delta$  is the distance between the leading edges of the two pulsed gradients;  $\gamma$  is the gyromagnetic ratio;  $S(G)$  is the signal under the influence of the pulsed gradients and  $S(0)$  is the signal without the pulsed gradients. After pixel-by-pixel calculation, an ADC map was obtained (16). Because the diffusion measurements are extremely sensitive to motion, the diffusion images were carefully scrutinized for effects of patient motion in the phase-encoding directions, and these effects were scored semiquantitatively as follows: 0 indicates no motion; 1, insignificant motion; 2, minor motion; 3, moderate motion; 4, significant motion; and 5, useless. Studies with scores of 4 or 5 were excluded. The water self-diffusion was measured in one axial section of the brain; the chosen section included the basal nuclei and the lateral ventricles (Figs 2 and 3). The ADC was calculated from circular regions of interest placed within the frontal and occipital subcortical white matter internal capsule, corpus callosum, frontal and occipital cortical gray matter, basal nuclei (nucleus lentiformis), and cerebrospinal fluid. The size of the regions of interest ranged from 10 to 32 pixels. The regions of interest with cortical gray matter were placed carefully to minimize inclusion of CSF and white matter.

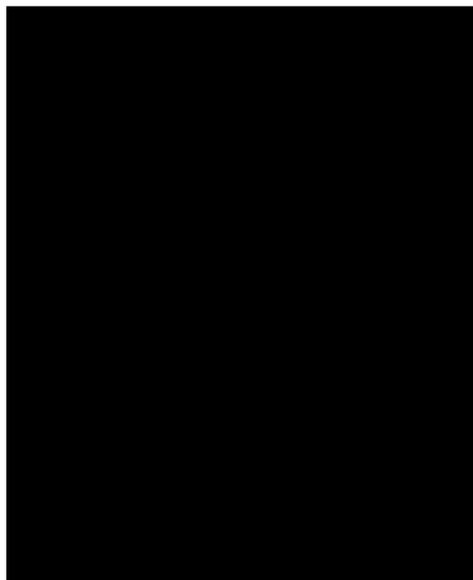


Fig 2. Calculated apparent diffusion map from a healthy 22-year-old woman (volunteer 6). High signal signifies high apparent diffusion; the diffusion image depicts diffusion perpendicular to the image plane. Note the low apparent diffusion within the corpus callosum, where the nerve fiber orientation is in the same plane as the image.

#### Statistics

To compare the ADC values obtained from different parts of subcortical white and gray matter, the Friedman two-way analysis of variance by ranks was used. For a comparison of the ADC values obtained in different regions of the brain of IIH patients with those of healthy volunteers, the Mann-Whitney U Test was used. A possible correlation between the ADC and the motion score was tested using a Spearman rank correlation test corrected for ties. The correlation between the ADC and the clinical signs was tested using a Pearson correlation analysis. The level of significance was chosen to be  $\leq .05$ .

#### Results

The initial symptoms of the 12 IIH patients were headache (11 patients), transient visual obscurations (8 patients), diplopia (4 patients), blurred vision (2 patients), and tinnitus (1 patient). The mean duration of symptoms was 22.3 months. The mean intracranial pressure was 26.0 mm Hg, the mean  $R_{\text{out}}$  was 17.6 mm Hg/mL per minute (Table 1), and 2 patients had B wave activity during the monitoring of intracranial pressure. As possible predisposing factors, 6 female patients weighed more than 25% above the ideal weight for women, 1 patient with epilepsy was under treatment with oxcarbazepine, known to induce hyponatremia, and 1 patient also had multiple myeloma. All findings

Fig 3. Calculated apparent diffusion maps from two patients with idiopathic intracranial hypertension (*A* is patient 4, *B* is patient 5); the window settings are the same as in Figure 2. The ADC within subcortical white matter is larger than in healthy volunteers.



appeared normal on conventional brain MR, with a normal or small ventricular system.

Calculated ADC maps from a healthy volunteer and an IIH patient are showed in Figures 2 and 3. In the group of healthy volunteers, eight had motion scores of 0, and four had motion scores of 1. The motion scores found in the patient studies are shown in Table 1. There was no statistically significant correlation between the motion scores and the calculated ADC values in the patient studies or in the control studies. We found no statistically significant regional differences between the ADC values measured within the frontal subcortical white matter and those measured within the occipital subcortical white matter; neither was any regional difference in the ADC values found between the frontal and the occipital cortical gray matter; con-

sequently we used the mean values for comparison. The mean calculated ADC values from the different brain regions in the patient group and in the control group are shown in Tables 1 and 2. In 7 of 12 patients, a mean ADC within subcortical white matter exceeding the mean ADC plus two standard deviations of the controls was found. The mean ADC in subcortical white matter in patients with IIH was statistically significantly increased compared with the mean ADC within subcortical white matter in the controls ( $P < .001$ ); excluding the patient studies with motion scores of 2 and 3, this difference was still statistically significant ( $P < .005$ ). No statistically significant differences were found between the two groups regarding ADC in the internal capsule, corpus callosum, nucleus lentiformis, and cortical gray matter.

TABLE 2: Healthy volunteers included in the study and the calculated values of the ADCs ( $\times 10^{-9}$  m<sup>2</sup>/s) in different brain regions

Volunteer/ age, y/sex	Subcortical White Matter	Cortical Gray Matter	Nucleus Lentiformis	Capsula Interna	Corpus Callosum	Cerebrospinal Fluid
1/25/M	0.82	1.58	1.38	2.13	0.41	3.27
2/24/M	0.59	1.06	0.26	1.34	0.26	2.90
3/23/F	0.79	1.28	0.77	1.41	0.18	2.85
4/26/M	0.73	1.13	1.04	1.40	0.26	2.89
5/39/F	0.58	1.36	1.16	1.27	0.15	3.14
6/22/F	0.63	1.14	0.87	1.63	0.23	3.07
7/35/M	0.64	1.21	0.80	1.28	0.32	2.98
8/58/F	0.78	1.32	0.91	1.75	0.26	3.11
9/28/F	0.75	1.47	0.68	1.20	0.24	3.16
10/30/M	0.82	1.72	1.26	1.71	0.30	3.24
11/73/M	0.88	1.36	0.91	1.34	0.27	3.05
12/66/M	0.95	1.47	1.36	1.39	0.26	2.97
Mean (SD)	0.75 (0.12)	1.34 (0.20)	0.95 (0.32)	1.47 (0.26)	0.26 (0.07)	3.05 (0.14)

TABLE 3: Patients with IIH examined serially: mean ADC ( $\times 10^{-9}$  m<sup>2</sup>/s)

Patient	Duration of Symptoms, mo	Subcortical White Matter	Cortical Gray Matter	Nucleus Lentiformis	Capsula Interna	Corpus Callosum	Cerebrospinal Fluid	Motion Score
2	1	0.77	1.15	0.86	1.38	0.20	3.03	0
2	5	1.29	1.56	1.54	1.78	0.38	2.98	2
2	9	1.27	1.57	1.02	1.53	0.65	3.01	0
9	1	1.30	1.99	1.30	1.85	0.42	3.21	3
9	5	1.09	1.35	1.08	1.94	0.49	3.07	2

There was a close correlation between the mean ADC in subcortical white matter and in the cortical gray matter in patients with IIH ( $P < .001$ ). Four of 7 patients with increased ADC in subcortical white matter also had a mean ADC in gray matter higher than the mean ADC plus two standard deviations of controls. There was no significant correlation between ADC in white matter and the duration of the symptoms; neither was any correlation found between ADC and  $R_{out}$ . A tendency was found toward a correlation between ADC and intracranial pressure ( $.05 < P < .1$ ).

Four months after the initial examination, patient 2 was reexamined because of continuing headache and visual obscurations despite treatment with diuretics and acetazolamide, and at this time mean intracranial pressure was 40 mm Hg. Four months later the patient was examined a third time, after a ventriculoperitoneal shunt operation. On the second examination, the ADC in white matter was increased over the 95% confidence interval for the controls, and the ADC in gray matter had also increased somewhat (Table 3). On the third examination, the ADC in white and gray matter were practically unchanged. Patient 9 was reexamined after 4 months, and the symptoms were in regression without medical treatment. The ADC in both white and gray matter was decreased at the second examination (Table 3); however, the ADC in white matter was still over the 95% confidence interval of the healthy controls.

## Discussion

Few clinical studies of brain water self-diffusion using MR have been reported so far. Tsurada et al (25) in a preliminary study found that the ADC values in arachnoid cysts were similar to those in stationary water, whereas the ADC of epidermoid tumors was similar to that in brain parenchyma. Increased ADC values have been reported in acute and chronic plaques in multi-

ple sclerosis (26, 27), and in a recent study increased ADC values were found in apparently normal white matter of patients with chronic multiple sclerosis (27). Recent studies of patients with cerebral infarction have reported decreased ADC values within the infarcted areas in the acute and subacute stages and increased ADC values in the chronic stage (28, 29).

Our study confirms previous findings, namely that the ADC within subcortical white matter in the brain is significantly greater in patients with IIH than in healthy controls (7). However, using the present method, we did not find significantly increased ADC within the internal capsule, corpus callosum, nucleus lentiformis, or cortical gray matter in the patient group, compared with the control group, although four patients had increased mean ADC in both white and gray matter. The correlation between ADC in subcortical white matter and cortical gray matter probably reflects partial volume effects, which are unavoidable given the section thickness when trying to place a region of interest selectively in cortical gray matter. In the previous study, the calculated ADC values in healthy volunteers were probably overestimated by some 30% to 85%, because of flow and brain motion. In the present study, the compensation for first-order bulk motion and pulsatile brain motion resulted in high signal-to-noise ratio and only very limited movement artifacts, which made it possible to calculate the ADC in absolute values and to make a direct comparison between the ADC of IIH patients and of healthy volunteers. The minor artifacts found in some patients and volunteers did not seem to influence the calculated ADC values, as no correlation was found between the motion score and the ADC in subcortical white matter in these two groups. The calculated ADC values in healthy volunteers are in good agreement with the findings of previous MR studies, which have reported ADC values within white matter ranging from 0.4 to  $1.1 \times 10^{-9}$  m<sup>2</sup>/s, within gray matter

ranging from 0.6 to  $2.0 \times 10^{-9}$  m<sup>2</sup>/s, and within CSF ranging from 2.9 to  $3.5 \times 10^{-9}$  m<sup>2</sup>/s (18, 19, 27, 30) in healthy volunteers.

Brain water self-diffusion is an anisotropic process within cerebral white matter; thus water self-diffusion is nearly unrestricted parallel to the nerve fibers, but restricted perpendicular to the nerve fiber orientation, whereas water self-diffusion is almost unrestricted within gray matter (30). This is also demonstrated by the ADC values obtained in the internal capsule and corpus callosum. In the present study the calculated ADC values represent the apparent water self-diffusion perpendicular to the axial plane. The regions of interest within subcortical white matter were placed in areas where the nerve fiber orientation is a mixture of both inplane and throughplane fibers, avoiding areas where the fiber orientation is purely inplane as in the corpus callosum, or purely throughplane as in the internal capsule.

Increased ADC within white matter signifies increased water mobility, which may be caused by an increase of the extracellular water fraction, as in demyelination (26, 27), or by an increased fraction of mobile water in the intracellular space (7, 31). An increased ADC value by a factor of 2 to 3, as we have found in seven patients, can not be explained by an increased extracellular water fraction alone; other possible explanations may be increased intracellular water mobility or an increase in the incoherent fluid motion caused by the increased intracranial pressure. In a previous study, no significant difference in T1 and T2 relaxation behavior was found between patients with IIH and healthy controls (7).

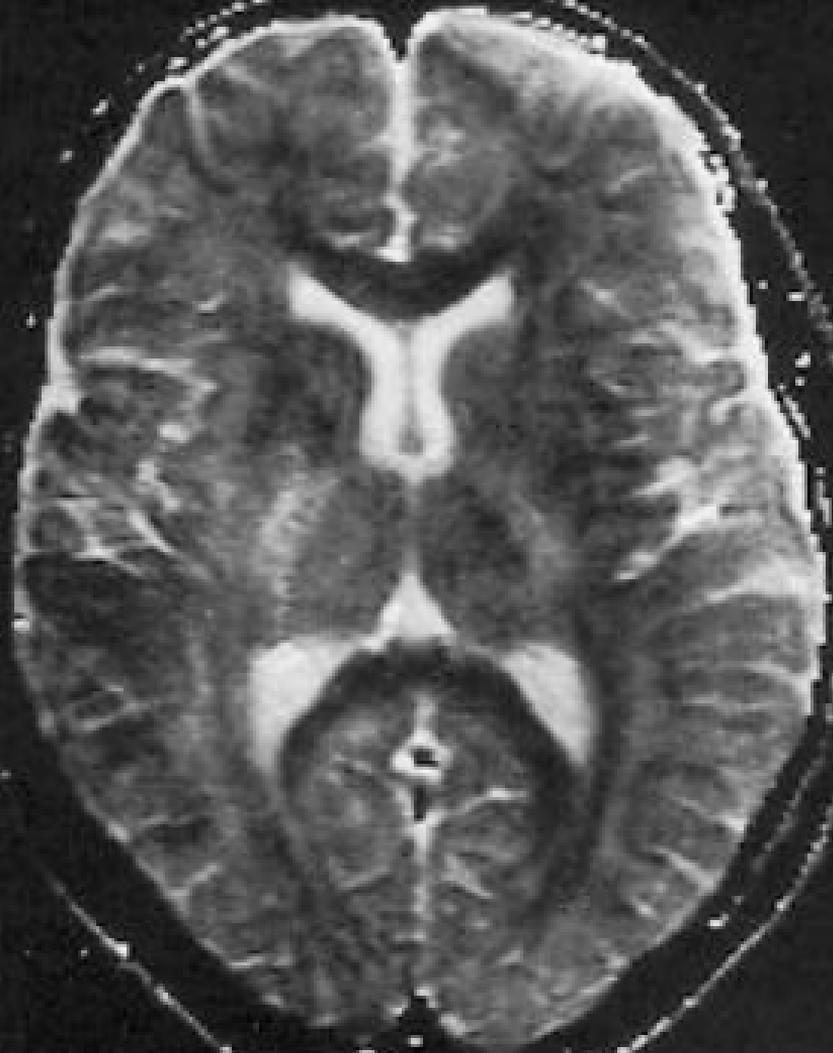
Increased cerebral blood volume has been suggested by some authors as a possible pathogenetic factor in the development of IIH (8, 32), but a recent study by Brooks et al using positron emission tomography (33) did not demonstrate increased cerebral blood volume in patients with IIH. Sahs and Joynt (34) suggested, based on brain biopsies in pseudotumor patients, that the cause of the disease is brain edema. This would lead to increased brain volume and a "stiff brain," which could explain why the ventricular system does not dilate despite an increased  $R_{out}$  (12, 24) and also confirms the normal or small ventricular system found in these patients. In nine of the patients with IIH an increased  $R_{out}$  was found, in agreement with previous studies (10–12). Increased  $R_{out}$  at the

level of the arachnoid villi and increased intracranial pressure usually cause hydrocephalus (24), but in the absence of ventricular dilatation, it may produce an interstitial edema, causing increased extracellular water volume. On the other hand, increased water accumulation in the brain would reduce the subarachnoid space over the cerebral hemispheres and thereby increase  $R_{out}$ . Both mechanisms could explain the increased ADC found within cerebral white matter in IIH patients. However, as mentioned we found no significant correlation between  $R_{out}$  and the mean ADC in white matter. The calculated ADC in subcortical white matter in patient 2 increased from a normal value on the first examination to values far exceeding the 95% confidence interval of healthy volunteers on the second and third examinations. This finding suggests that the duration of the symptoms could have an influence on the ADC; however, we found no correlation between ADC in subcortical white matter and the duration of symptoms. This could be caused by the IIH patients' being in different stages of disease activity: some patients were in progression, others were in regression. In patient 9, ADC in subcortical white matter was considerably increased on the first examination, and although it was lower on the reexamination 4 months later, ADC still exceeded the 95% confidence interval of healthy volunteers. During these 4 months the symptoms of this patient regressed on a banting diet alone. In five patients the calculated ADC values were within the range of the control group; however, we found no apparent differences between these five patients and the seven patients with elevated ADC within subcortical white matter. This probably reflects the heterogeneity of IIH syndromes, which are probably not one single disease entity.

In conclusion, a significantly increased ADC was found within white matter of the brain in 7 of 12 patients fulfilling the diagnostic criteria for IIH; however, we found no correlation between mean ADC values in white matter and  $R_{out}$  or between ADC in white matter and the duration of symptoms. The finding of increased water mobility within white matter in patients with IIH does not provide us with an explanation of the causes of this disease, but it does demonstrate the feasibility for noninvasive studies of this patient group to assess the clinical significance of these preliminary findings.

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