SHORT REPORT

Diffuse brain oedema in idiopathic intracranial hypertension: a quantitative magnetic resonance imaging study

M E Bastin, S Sinha, A J Farrall, J M Wardlaw, I R Whittle

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authors' affiliations
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Correspondence to:
Dr Mark Bastin, Medical
and Radiological Sciences
(Medical Physics),
University of Edinburgh,
Western General Hospital,
Crewe Road, Edinburgh
EH4 2XU, UK; meb@
skull.dcn.ed.ac.uk

Objectives: To investigate the hypothesis that idiopathic intracranial hypertension is associated with diffuse brain oedema, using quantitative magnetic resonance imaging.
Methods: Values for the mean diffusivity of water (<D>) and the proton longitudinal relaxation time (T1) were measured for various brain regions in 10 patients with idiopathic intracranial hypertension and 10 age, sex, and weight matched controls.
Results: No significant differences in <D> and T1 values were found between patient and control groups in any of the brain regions investigated.
Conclusions: The results suggest that idiopathic intracranial hypertension is not associated with abnormalities of convective transependymal water flow leading to diffuse brain oedema.

I diopathic intracranial hypertension (IIH), also known as pseudotumour cerebri, is a chronic disorder of unknown aetiology which is characterised by raised intracranial pressure. The features of this condition—which typically affects young obese women—are headache, visual disturbance, and papilloedema in the absence of abnormalities on structural magnetic resonance (MR) imaging and in cerebrospinal fluid (CSF) composition.[1–4] Potential mechanisms underlying IIH include brain swelling caused by diffuse brain oedema, increased sagittal sinus venous pressure, increased cerebral blood volume, increased rate of CSF production, and disturbance of CSF circulation.[5 6]

The presence of diffuse brain oedema and its role in the raised intracranial pressure associated with IIH can be assessed non-invasively using MR imaging techniques that characterise the properties of brain water. Two such methods are diffusion weighted MR imaging (DW-MRI) and quantitative mapping of the proton longitudinal relaxation time (T1). In the former technique, the mean diffusivity (<D>), which reflects the average microscopic mobility of brain water molecules, can be determined from an MR imaging experiment in which diffusion sensitising gradients are applied in three orthogonal directions.[7] Quantitative maps of T1 provide useful information on the spatial distribution of brain water content.[8]

In this paper we report results from a pilot study in which MR imaging was used to measure values of <D> and T1 for various different brain regions in 10 patients with IIH and in a control group of age, sex, and weight matched volunteers. By directly comparing these quantitative MR imaging parameters in the two subject groups it is possible not only to investigate the hypothesis that IIH is caused by diffuse oedema and brain swelling, but also to identify which regions, if any, are affected by changes in brain water homeostasis.

METHODS

Subjects

Ten female patients with a clinical diagnosis of IIH and no contraindications to MR were recruited consecutively from neurology and ophthalmology clinics and enrolled in the study. The diagnostic criteria for IIH were fulfilled in all cases; these are:

- increased mean intracranial pressure measured by lumbar puncture, and greater than 20 cm H_2O;
- no evidence of focal or diffuse disease from the radiological data;
- no evidence of major venous sinus thrombosis on MR venography;
- normal protein concentration and normal cell count in the CSF.

All patients were symptomatic, with headache or visual disturbances or both. Two patients had lumboperitoneal shunts but these were confirmed on clinical and lumbar puncture examination to be non-functional. None of the patients was undergoing corticosteroid treatment. Ten healthy women matched for age and weight, and with no history of neurological disease, were also recruited as controls.

The local ethics committee approved the study and informed consent was obtained from each subject.

MR imaging acquisition parameters

All MR imaging data were obtained using a GE Signa LX 1.5 T clinical scanner (General Electric, Milwaukee, Wisconsin,

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Abbreviations: ADC, apparent diffusion coefficient; DW-MRI, diffusion weighted magnetic resonance imaging; EP, echo planar; IIH, idiopathic intracranial hypertension; IR, inversion recovery; ROI, region of interest; TI, inversion time

USA) and manufacturer-supplied "birdcage" quadrature head coil. Each patient underwent MR imaging, which consisted of a standard fast spin echo T2 weighted sequence, DW-MRI and T1 mapping protocols. The duration of the examination was approximately 20 minutes.

In the DW-MRI experiment, DW images were acquired using a single shot, spin echo, echo planar (EP) imaging sequence in which two symmetric trapezoidal gradient pulses of duration $\delta = 32.2$ ms, separation $\Delta = 39.1$ ms, and rise time $\varepsilon = 1.2$ ms were inserted around the 180° refocusing pulse in the required gradient channel. Sets of axial DW-EP images (b = 0 and 1000 s/mm^2) were collected with diffusion gradients applied sequentially along the superior/inferior, anterior/posterior, and right/left directions. Two acquisitions consisting of a baseline T2 weighted EP image and three DW-EP images, a total of eight images, were collected per slice position. The acquisition parameters for the DW-EP imaging sequence were 15 axial slices of 5 mm thickness and 1 mm slice gap, a field of view of 240×240 mm, an acquisition matrix of 128×128 (zero filled to 256×256), a TR (time of repetition) of 10 s, and a TE (time of echo) of 98.8 ms.

Maps of T1 values were obtained from 15 axial slices coincident with those imaged in the DW-MRI experiment using an inversion recovery (IR) single shot spin echo EP imaging sequence. To provide accurate values of T1, nine different inversion times (TI) were chosen—namely 50, 220, 760, 1300, 1840, 2380, 2920, 3460, and 4000 ms.[9] The remaining acquisition parameters for this IR-EP sequence were identical to those used in the DW-MRI experiment, except for a TR of 60 s.

Image analysis

In the DW-MRI experiment, the set of two component EP images for each gradient direction was averaged to give four (one T2 weighted and three DW-EP images) high signal to noise ratio images for each slice. Within each voxel the three orthogonal apparent diffusion coefficient (ADC) components (ADC_x, ADC_y, and ADC_z) were estimated by linear regression from the measured signal intensities in the EP images. To avoid diffusion anisotropy effects,[7] the three orthogonal ADC components were averaged to produce <D>.

The value of T1, the cosine of the inversion pulse flip angle (κ), and the equilibrium signal intensity (S_0) were determined for every voxel from the set of nine IR-EP images collected in each of the 15 slice locations using the equation[9–11]: $S(S_0, \kappa, T_1) = S_0[1 - (1 - \kappa)e^{-(TI/T1)}]$

Region of interest and statistical analysis

To determine whether there were significant differences in brain water diffusion and proton longitudinal relaxation time parameters between the patient and control groups, a region of interest (ROI) analysis, similar to that employed by Gideon et al,[12] was undertaken for various grey and white matter structures—specifically, cortical grey matter, thalamus, head of the caudate nucleus, putamen, corpus callosum, posterior limb of the internal capsule, subcortical white matter, and centrum semiovale. Values of <D> and T1 were obtained from multiple small circular (25 voxels, volume 110 mm^3) ROI placed bilaterally in these brain structures (fig 1A). Partial volume effects were minimised by siting the ROI at least 3 voxels away from the edge of the ventricles and sulci. So that the observer was not influenced by values of the diffusion and relaxation time parameters, all ROI were defined on the T2 weighted EP images. As the T2 weighted EP images and the <D> and T1 parametric maps were by definition coregistered, this allowed these quantitative parameters to be measured simultaneously in each ROI. The observer (AJF) was blind to the clinical status of each subject and the purpose of the study.

For the patient and control groups, descriptive statistics were determined for the <D> and T1 parameters in each ROI from the combined measurements made from each population. Statistical differences in these parameters between the two groups were assessed using an independent samples two tailed Student t test (null hypothesis, <D>(patient)−<D>(control) = 0, etc). In all cases a probability (p) value of <0.05 was considered statistically significant.

RESULTS

The age and weight ranges for the patient group were 16 to 49 years (mean (SD), 28.0 (10.0) years) and 63.5 to 127.0 kg (92.2 (23.9) kg). The mean duration of symptoms was 31.5 (22.7) months. The age and weight ranges for the controls were 18 to 41 years (29.0 (7.4) years) and 71.0 to 112.0 kg (92.6 (14.6) kg). There was no significant difference between the mean age and weight of the patient and control groups.

Table 1 shows values of <D> and T1 for the patient and control groups in each of the brain regions investigated. In these data there is no evidence for an increase in brain water diffusion and proton longitudinal relaxation time values in the patient group compared with the controls. In fact there was no statistically significant difference in either parameter in any region between the two subject groups. Also shown for comparison are published values of these parameters obtained from previous studies in normal volunteers. In all the regions investigated there is close agreement between the values of <D> and T1 measured in the current study and those reported previously.[10] [13] [14]

DISCUSSION

There have been several recent reviews of the mechanisms underlying IIH.[5] [6] Despite extensive studies of these mechanisms the relative contributions of each still remain unclear. In this paper the possible role of diffuse brain oedema in increasing cerebral volume was investigated by comparing brain water diffusion and proton longitudinal relaxation time values in patient and control groups.

There have been three previous studies of brain water diffusion parameters in IIH. Sorensen et al found evidence for increased diffusion in various brain regions in seven patients with IIH when compared with measurements made in a group of healthy controls.[15] Specifically, increased water diffusion was observed in periventricular regions in three patients, and in the whole brain in the remaining four. These general results were replicated in a larger study of 10 patients and controls.[16] It was argued that these data indicated that IIH is associated with abnormalities of convective transependymal water flow leading to diffuse brain oedema. Such a hypothesis is, however, not conclusively supported by the data obtained by Gideon et al in their study of 12 patients and 12 controls,[12] where significantly increased water diffusion values were found only in subcortical white matter and not in other parenchymal regions. Nevertheless, in these three studies, IIH patients were found to have significantly higher ADC values than controls in some brain regions—a difference that was not observed in the current study.

The reason for this apparent discrepancy could arise from two main sources, namely differences in the subject populations and in the MR imaging protocols. Gideon et al,[12] for example, imaged seven women and five men with IIH of mean age 38.6 (16.7) years and mean symptom duration of 22.3 (25.9) months. Although the mean age of our patient sample was younger (at 28.0 (10.0) years) with longer symptom duration (31.5 (22.7) months), none of these differences is statistically significant. Furthermore, sex differences in the patient populations can also be discounted, as three of the seven women scanned by Gideon et al had
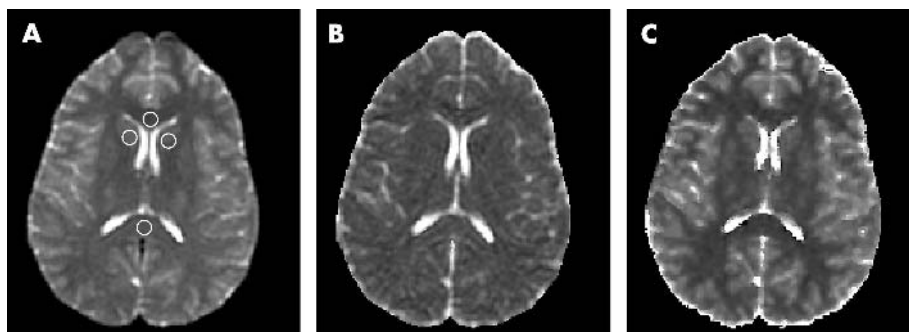
Figure 1 (A) T2 weighted echo planar (EP) image. (B) Mean diffusivity (<D>) and (C) proton longitudinal relaxation (T1) parametric maps obtained from a 19 year old female patient. The small circular regions of interest used to measure water diffusion and proton relaxation time parameters in the various brain regions (in this case head of the caudate nucleus and corpus callosum) are overlaid on the T2 weighted EP image.

raised ADC values in subcortical white matter. It should be noted, however, that the controls recruited by Gideon were not weight matched to the patients as in the current study. It is therefore unclear whether differences in the subject populations are really responsible for the contradictory results of these studies.

The difference between the MR imaging protocols employed in these studies is, however, much more significant. Specifically, in the three studies done by Sorensen et al [15] [16] and Gideon et al,[12] diffusion parameters were measured using spin echo sequences with diffusion gradients applied in a single direction. While spin echo sequences can provide accurate ADC maps, any bulk patient motion will introduce significant artefacts into the component DW images. More importantly, it is now well recognised that the accurate measurement of the magnitude of water diffusion in vivo requires that the effects of diffusion anisotropy are removed.[7] [14] This is typically achieved by averaging the ADC values obtained from an MR imaging experiment in which diffusion sensitising gradients are sequentially applied in three orthogonal directions. By applying diffusion gradients in only one direction, it is unclear whether any observed differences between subjects reflect pathological changes or merely biological variation in fibre tract orientation and subject positioning in the magnet. In the current study the use of single shot EPI significantly reduces bulk patient motion, while <D> is calculated from ADC components measured in three orthogonal directions.

Our study was undertaken to investigate whether there were gross differences in brain water diffusion parameters and proton longitudinal relaxation time values between IIH patients and suitably matched controls. Table 1 shows that in our sample population no such gross differences exist. Furthermore, the similarity between the values of <D> and T1 displayed in table 1 suggests that to detect a significant difference at this level would require a very large sample size. For example, a study with 80% power to detect a significant difference ($p<0.05$) in <D> values of subcortical white matter between patient and control groups would require 1014 subjects. However, although the methodology of the current study is more refined than that of Sorensen et al and Gideon et al, it is also possible that heterogeneity in the pathogenesis of IIH is responsible for the contradictory results of these studies.[6]

Conclusions

In this pilot study, brain water diffusion and proton longitudinal relaxation time parameters were measured in a small cohort of patients with idiopathic intracranial hypertension and controls to determine whether increased brain water was associated with this condition. No significant difference was found between these MR parameters in the two groups, which suggests that diffuse brain oedema is not a feature of IIH.

Table 1 Mean diffusivity (<D>) and proton longitudinal relaxation time (T1) measured in various brain regions for 10 female patients with idiopathic intracranial hypertension and 10 age, sex, and weight matched controls

Brain region	<D> ($\times 10^{-6}$ mm^2/s)				T1 (ms)			
	Patient	Control	p Value	Published values[a]	Patient	Control	p Value	Published values[c]
Grey matter								
Cortical grey matter	842 (124)	816 (92)	0.28	930 (20)	1024 (146)	1070 (221)	0.27	1113 (48)
Thalamus	738 (30)	719 (38)	0.20	730 (50)	852 (60)	835 (44)	0.29	814 (26)
Caudate (head)	764 (34)	771 (45)	0.62	680 (70)	1075 (71)	1103 (73)	0.23	1033 (41)
Putamen	727 (30)	708 (38)	0.20	720 (90)	1059 (96)	1040 (80)	0.49	919 (42)
White matter								
Corpus callosum	818 (85)	824 (102)	0.84	815 (117)	880 (179)	812 (120)	0.16	756 (81)
Internal capsule	772 (65)	762 (33)	0.51	690 (30)	834 (133)	848 (94)	0.71	–
Subcortical WM	720 (44)	726 (52)	0.58	770 (30)	748 (72)	733 (43)	0.27	642 (21)
Centrum semiovale	678 (52)	662 (65)	0.42	(648 (24))[b]	729 (46)	742 (30)	0.31	–

Values are mean (SD).
[a]Values <D> reported by Ulug and van Zijl in five normal volunteers.[13]
[b]Values of <D> reported by Pierpaoli et al in eight normal volunteers.[14]
[c]Values of T1 reported by Kingsley et al in three normal volunteers at 1.5 T.[10]

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Authors' affiliations
M E Bastin, Medical and Radiological Sciences (Medical Physics), University of Edinburgh, Edinburgh, UK
S Sinha, A J Farrall, J M Wardlaw, I R Whittle, Clinical Neurosciences, University of Edinburgh

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