Regional changes in hippocampal T2 relaxation and volume: a quantitative magnetic resonance imaging study of hippocampal sclerosis

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Abstract

Objective—The principal MRI features of hippocampal sclerosis are volume loss and increased T2 weighted signal intensity. Minor and localised abnormalities may be overlooked without careful quantitation. Hippocampal T2 relaxation time (HT2) can be quantified, but previously has only been measured on a few thick coronal slices with interslice gaps. In this study HT2 was measured along the entire length of the hippocampus on contiguous slices and used, with quantitative measures of hippocampal volume (HV) and distribution of atrophy, to better define the range of hippocampal sclerosis.

Methods—Thirty patients with temporal lobe epilepsy, 10 patients with extratemporal localisation related epilepsy and extratemporal lesions, and 20 control subjects were studied using MRI T2 relaxometry and volumetry.

Results—In controls and patients, HT2 was higher in the anterior than the posterior hippocampus. Using HV, morphometric, and HT2 data, patients with temporal lobe epilepsy were classified as unilateral diffuse hippocampal sclerosis (n=16), unilateral focal (n=6), bilaterally affected (n=6), and normal (n=2). In patients with unilateral hippocampal sclerosis, the anterior hippocampus was always affected. In three patients with normal HV, HT2 measurements disclosed unilateral focal abnormalities that corresponded to the EEG lateralisation of epileptic activity. Patients with bilateral hippocampal involvement had an earlier onset of epilepsy than patients with unilateral hippocampal sclerosis.

Conclusions—Measurement of regional abnormalities of HT2 along the length of the hippocampus provides further refinement to the MRI assessment of the hippocampi in patients with temporal lobe epilepsy and is complementary to volumetric and morphological data.

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The detection of hippocampal sclerosis in patients with medically intractable temporal lobe epilepsy is important because hippocampal sclerosis is the most common underlying pathology seen in these patients and is

associated with a 60% chance of the patient becoming seizure free postsurgically.¹ Histopathological and MRI studies have shown differences in the regional distribution of hippocampal sclerosis, indicating a range for the pathology.²⁻⁴

MRI features suggestive of hippocampal sclerosis are an increased signal on T2 weighted images, volume loss, loss of internal structure and a decreased signal on T1 weighted images.⁵⁻¹⁰ Hippocampal volume (HV) loss ipsilateral to seizure onset in EEG was shown pathologically to be hippocampal sclerosis.⁴⁻⁶ Focal atrophy may also be detected³ and, with correction of HV for intracranial volume (ICV), bilateral hippocampal atrophy may be inferred.⁴⁻¹¹ Hippocampal volumes measured by MRI, however, have been reported to be normal in a subgroup of patients with pathologically confirmed hippocampal sclerosis.¹⁰

Visually assessed hippocampal hyperintensity on T2 weighted images was found in about 40% of cases of hippocampal sclerosis with a range from 8% to 70% in other studies.¹² In contrast to this variability, hippocampal T2 relaxation time (HT2)—as the source of this contrast in MRI—can be measured reliably and reproducibly.¹²⁻¹³ Previous studies have shown subtle changes of HT2 and inverse correlations between HT2 and HV in hippocampal sclerosis.⁴⁻¹⁴⁻¹⁵

The quantitation of morphological changes and increased T2 signal intensity permits assessment of the severity and topographical extent of hippocampal sclerosis. Focal atrophy and change in T2 signal may be overlooked by visual inspection especially if only a few slices are used.³ Until recently, HT2 has been measured on one slice using a multiecho sequence⁴⁻¹²⁻¹⁴⁻¹⁶ or on a few thick slices with interslice gaps.¹⁵ By using an interleaved, multislice, standard dual echo sequence of the type found on all commercial scanners, we obtained images for visual assessment and measurement of T2 values, covering the whole brain in 10 minutes.¹³ The aim of this study was to measure HT2 throughout the whole length of the hippocampi and correlate these values with morphometric data of the hippocampi, to better define the range of hippocampal sclerosis.

Methods

SUBJECTS

Analysis of MRI was carried out blinded to the clinical data. We scanned a control group of 20 healthy volunteers (median age 31 years, range

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20–59 years; 11 women, nine men). During the same time period, 30 consecutive patients (median age 34 years, range 19–49 years; 16 women, 14 men) with medically intractable temporal lobe epilepsy without any foreign tissue lesion on MRI, who were referred for pre-surgical evaluation at the epilepsy centre of the National Hospital for Neurology and Neurosurgery, London, were investigated. Fourteen of these patients have had surgery for epilepsy so far. The median age of onset of the epilepsy was 7.5 years (range 1–37 years) and the median duration 24 years (range 6–42 years). All patients had complex partial seizures with a median frequency of 7/month and clinically lateralising features (such as ictal unilateral dystonic posturing and speech disturbances). In eight patients (27%) this was obtained on history from reliable witnesses and in 22 (73%) on video-EEG recordings. Twenty seven patients (90%) had consistent lateralised and localised interictal epileptic activity on prolonged EEG recordings, 22 (73%) had clearly demonstrated ictal EEG foci. Twenty two patients (73%) had secondarily generalised tonic clonic seizures, 18 of whom had more than 10 during their lifetime. Twelve patients (40%) had a history of complicated febrile convulsions, and five (17%) a history of meningitis or encephalitis.

Ten patients with extratemporal partial seizures (median age 39.5 years, range 22–49 years, two women, eight men) were also investigated. The median age of onset in this group was nine years (range 2–44 years), and the median duration of epilepsy was 31 years (range 1–36 years). All had discrete extratemporal lesions: neoplastic (n=4), vascular (n=3), or developmental (n=3) and consistent seizure semiology. Seven patients had simple partial seizures and five had complex partial seizures. The median frequency of the partial seizures was 8/month. Seven patients also had secondarily generalised tonic clonic seizures, of whom five had more than 10 during their lifetime. All 10 patients had prolonged EEG recordings. Six patients had lateralised and localised interictal epileptiform activity, a further one had ictal findings that were consistent with the structural lesions. Two patients had complicated febrile convulsions and one had meningitis.

QUALITATIVE MRI ASSESSMENT

The MR images were acquired on a 1.5 T GE Signa MR scanner. The total examination time was 30 minutes. Visual inspection of hippocampi by two experienced neuroradiologists used oblique coronal T1 weighted images perpendicular to the long axis of the right hippocampus (IR prepared SPGR, TR/TE/TI/NEX 17.4/4.2/450/1, flip angle 20°, matrix size 256×192, 24×18 cm FOV, 124 slices, slice thickness 1.5 mm, scan time 7 minutes), oblique coronal proton density and T2 weighted spin echo images (TR/TE1/TE2/NEX 2000/30/120/1, 256×192 matrix, 24×18 cm FOV, 5 mm slices with no gap, scan time 10 minutes), and coronal oblique fast FLAIR images (TR/TE/TI/NEX 11000/144/2600/1, 256×192 matrix, 24×18 cm FOV, 5 mm slices

with no gap, scan time 8 minutes). The visual detection of hippocampal sclerosis was based on the criteria of unilateral or bilateral small hippocampi on T1 weighted images and increased signal on T2 weighted and fast FLAIR images and was carried out blind to clinical data.

HIPPOCAMPAL T2 (HT2) MAPPING

For computation of T2 values, the conventional spin echo sequence (parameters as above) was obtained by two interleaved acquisitions to cover the entire brain. Contiguous slices were obtained in a tilted coronal plane that was perpendicular to the long axis of the hippocampi. Image data were transferred from the scanner to a Sun workstation. Pixel by pixel T2 maps were calculated from the images, using the expression $T2 = (TE2 - TE1) / (\ln(S1/S2))$, where S1 and S2 are the signal intensity in the early and late echo images, with echo times TE1 and TE2 respectively. This technique has recently been validated including repeated acquisitions of data and measures of intrarater and interrater and test-retest reliability in controls and patients.¹³ HT2s were measured by the same observer using DispImage image analysis software¹⁷ by placing the largest possible elliptical region of interest within the hippocampus, avoiding hippocampal boundaries, and starting posteriorly (fig 1). The first slice was defined as the one anterior to the slice in which the fornix was seen in its greatest length. Regions of interest were placed on four to six consecutive slices anteriorly, because of variation in hippocampal length, thus covering the whole length of the hippocampus. Complete HT2 measurement took 10 minutes a case.

Intrarater and interrater variability of HT2 measures using this method were assessed by calculation of the limit of agreement and coefficient of repeatability.¹⁸ Intrarater repeatability of HT2 measurements in all hippocampal slices in 20 control subjects and 10 patients with temporal lobe epilepsy showed a mean difference of 0.34 ms (<1% of the mean HT2), a limit of agreement of 4 ms, and a coefficient of repeatability of 4.5%. Interrater repeatability in 20 controls and 10 patients showed a mean difference between raters of 0.23 ms. The limit of agreement was 5.1 ms, giving a coefficient of repeatability of 5.7%.

HIPPOCAMPAL VOLUMETRY

For volumetric studies, the IR-P-SPGR sequence (parameters as above) was used. All HV measurements were made by the same observer. After reformatting the 3D data set in a plane perpendicular to the long axis of the right hippocampus, the hippocampal volume was estimated by measuring the area of the hippocampus on contiguous 1.5 mm thick coronal slices throughout the whole anterior-posterior extent by using manually drawn boundaries (fig 1).¹⁷

Reproducible landmarks were used, as described previously, to include the CA1 to CA4 sectors of the hippocampus, the dentate gyrus, the subiculum, and the alveus starting posteri-

Figure 1 Coronal T2 maps (top) and IR-P-SPGR images (bottom) showing the temporal lobes and the hippocampi of a control subject at different anteroposterior locations—the tail (left) and the head (right). On the T2 maps the ROI for the HT2 measurement and on the IR-P-SPGR images the in plane boundaries of the hippocampus as manually traced are shown.

only on the slice which showed the crus of the fornix in its greatest length.^{3 19} The HV was calculated by multiplying the slice thickness with the sum of the hippocampal cross sectional areas (Cavalieri's principle). Hippocampal volume ratios (HVRs) were calculated as ratio of the volume of the smaller divided by the volume of the larger hippocampus. HV was corrected for head size using the intracranial volume (ICV) and a covariance estimate as described previously.^{20 21} Corrected hippocampal volume is referred to as HV_c. Complete volumetric assessment took 30–40 min/case.

Intrarater repeatability studies were carried out in 10 patients with temporal lobe epilepsy and 10 controls. There was a mean difference of HV of 7.0 mm (<1% of the mean HV) and limit of agreement of 268.9 mm—that is, a coefficient of repeatability of 8.4% of the mean HV.

CLASSIFICATION OF HIPPOCAMPI AS NORMAL OR ABNORMAL ON HV_c AND HT2

The normality of a hippocampus was decided by using the normal range of HT2, HV_c, and HVR, defined as the control mean $\pm$ 2 SD. The abnormalities were classified as unilateral if one hippocampus had no abnormal values of HV_c

and HT2, and bilateral if HV_c or HT2 were abnormal on both sides.

GRAPHS OF DISTRIBUTION OF THE HT2 AND OF HV AND THEIR CLASSIFICATION

Measurements of HT2 were plotted as a function of slice position (table 1, figs 2–4). Slice position 1 was the most posterior and because of variation of hippocampal length four to six slices covered the different hippocampi. Values for HT2 were compared with a normal range covering $\pm$ 2 SD of the control mean. Hippocampal cross sectional areas were also plotted as a function of slice position. Slice position 1 was the most posterior and because of variation of hippocampal length 25–29 slices covered the different hippocampi. Regional atrophy was identified by side to side comparison, and comparison with graphs of hippocampal cross sectional areas covering a total volume which was 2 SD above and below the control mean.⁴

The distribution of abnormalities of HV and HT2 was reviewed and classified in a blinded fashion by two independent raters, as diffuse or focal. A focal abnormality was defined as affecting less than two thirds of the length of the individual hippocampus—that is, the corresponding number of slices used for T2 or volumetric measurement. A diffuse abnormality was defined as affecting more than two thirds of the length of the individual hippocampus.

STATISTICS

Linear regression analysis was used to normalise hippocampal volumes for intracranial volume. Mean values were compared using *t* tests,

Table 1 Posteroanterior gradient of hippocampal T2 in control subjects

Slice position	1 (posterior)	2	3	4	5	6 (anterior)
Mean HT2 (ms)	84.3	84.9	85.1	85.5	86.1	86.9
SD (ms)	2.3	3.2	3.2	2.6	2.7	3.2

Mean HT2 values of 40 hippocampi in 20 control subjects as a function of the position of contiguous 5 mm thick coronal slices. Mean HT2 values were higher in the anterior part of the hippocampi (ANOVA, *p*=0.003). Slice position 1 is the posterior hippocampus.

Figure 2 Unilateral focal anterior hippocampal sclerosis. The quantitative data show a left anterior involvement which was missed by visual inspection. HVR=0.8 (normal >0.93), HV_c left=2382 mm³ (normal >2772 mm³), HV_c right=3074 mm³ (normal >2694 mm³). On the distribution graphs, the black circles represent the left hippocampus and the open squares the right hippocampus. Dotted lines indicate normal range (control mean $\pm$ 2 SD).

Figure 3 Diffuse right hippocampal sclerosis. Diffuse abnormalities were more evident on the distribution graph of the cross sectional areas than on the HT2 distribution graph which was only abnormal in the anterior hippocampus. HVR 0.73 (normal >0.93), HV_c left=3471 mm³ (normal >2772 mm³), HV_c right=2614 mm³ (normal >2694 mm³). On the distribution graphs, the black circles represent the left hippocampus and the open squares the right hippocampus. Dotted lines indicate normal range (control mean $\pm$ 2 SD).

Mann-Whitney *U* test, Wilcoxon test, analysis of variance (ANOVA), and Kruskal-Wallis ANOVA as appropriate to the variances, the normality of the distributions, and whether data were paired or not. Categorical data were tested for association using Fisher's exact test. Analysis was carried out using SPSS 6.1 for Windows.

Results

A complete MRI data set consisted of visual assessment, HT2, HVR, HV_c , and graphs of HV_c and HT2 distribution.

CONTROL SUBJECTS

No abnormalities were detected by visual assessment.

In the control group we could measure HT2 on six consecutive hippocampal slices. There were no differences between HT2 on the left and on the right side. Mean HT2 values were higher in the anterior part of the hippocampi ($p=0.003$) (table 1). We therefore established normal values and the limits of the reference range for each of the six slice positions separately. There was no correlation between HT2 and age or sex.

Values for HT2 were plotted as a function of slice position. The slice which showed the anterior part of the brainstem used as a reference structure in a previous study⁴ was found on slice positions 3, 4, and 5.

Mean HVR (SD) was 0.97 (0.02). The lower reference limit for normal HVR was taken as 0.93, 2 SD below the control mean. HVR in female and male controls did not differ significantly.

There were no sex differences in HV_c after normalisation for ICV. Mean HV_c (SD) was 3184 mm³ (245 mm³) on the right and 3200 mm³ (214 mm³) on the left. The lower reference limit for normal HV_c was 2694 mm³ for the right hippocampus and 2772 mm³ for the left hippocampus. There was no significant difference between the right and left HV_c before or after correction for ICV.

Most hippocampi in control subjects were covered by 25 1.5 mm thick slices, in five subjects they were one to four slices longer than this. In six subjects the numbers of slices covering the whole hippocampus differed from side to side by one slice (with a thickness of 1.5 mm). Hippocampi were aligned at the fornices

Figure 4 Bilateral hippocampal pathology. Morphological studies indicate diffuse loss of right hippocampal volume. HT2 are bilaterally abnormal. HVR 0.68 (normal >0.93), HV_l left=3258 mm³ (normal >2772 mm³), HV_r right=2191 mm³ (normal >2694 mm³). On the distribution graphs, the black circles represent the left hippocampus and the open squares the right hippocampus. Dotted lines indicate normal range (control mean $\pm$ 2 SD).

and consequently this asymmetry was most apparent in the anterior hippocampi.

PATIENTS WITH TEMPORAL LOBE EPILEPSY

Visual assessment of T1 weighted, T2 weighted, and fast FLAIR images by two experienced neuroradiologists identified 21 patients with unilateral volume loss and/or high T2 weighted signal, four patients with bilateral abnormalities, and five patients without any abnormality.

Using the normal ranges of HVR, HV_l, and HT2 we identified 22 patients with unilateral abnormal values, six patients with bilateral abnormalities, and two patients with normal hippocampi (fig 5). Fourteen patients have had anterior temporal lobe resections so far and pathology showed severe neuronal loss and gliosis in hippocampal subfields CA1 and CA3 in all cases. Twelve of these 14 patients were

from the group with unilateral changes on quantitative MRI, two patients were from the bilaterally affected group of this study.

The profiles of HT2 and HV demonstrated unilateral focal anterior (n=6) (fig 2), unilateral diffuse hippocampal sclerosis (n=16) (fig 3), bilaterally affected (n=6) (fig 4), and normal hippocampi (n=2). In the patient group we could measure HT2 on four to six consecutive hippocampal slices and by the same number of HT2 slices on both sides in 25 of 30 patients. In the remaining five, HT2 was measurable on one more slice on one side. The HV was calculated from 21 to 27 1.5 mm thick slices (median 23 slices). In 18 of 30 patients the two hippocampi differed in length by 1.5–6 mm. Regional abnormalities of HT2 were more evident than regional morphological changes in 10 of the 30 cases (see the example in fig 4 in which HT2 is abnormal bilaterally and HV

Figure 5 MRI assessment of 30 patients with temporal lobe epilepsy (TLE). Quantitative analysis of hippocampal T2 (HT2) values and volume (HV) measurements and analysis of HT2 and HV as functions of slice position (profiles) to define the range of hippocampal sclerosis (HS).

Table 2 Clinical features of patients with MRI defined subgroups of hippocampal sclerosis and normal MRI

	Unilateral focal	Unilateral diffuse	Bilateral	Normal MRI
Number of patients	6	16	6	2
Age (y, median (range))	37.5 (30–42)	33.5 (19–49)	33 (27–44)	41 (34–48)
Duration of epilepsy (y, median (range))	22 (10–39)	21 (6–40)	29 (18–42)	14.5 (11–18)
Age of onset of epilepsy (y, median (range))*	14 (2–23)	7.5 (1–24)	2.5 (2–13)	26.5 (16–37)
Number (%) of patients with:				
Febrile convulsions	2 (33)	7 (44)	3 (50)	0
Meningitis/encephalitis	0	5 (31)†	0	0
> 10 SGS/lifetime	2 (33)	8 (50)	6 (100)‡	1
CPS/month (median)	4	13	5	11

* $p=0.05$; † $p=0.04$; ‡ $p=0.02$.

The age of onset differed significantly between groups of patients with temporal lobe epilepsy and different categories of hippocampal sclerosis. SGS=secondarily generalised seizures, CPS=complex partial seizures.

abnormal on the right side only). In two unilaterally and two bilaterally affected cases, however, morphological abnormalities were more evident (fig 3).

In detail, visual inspection reported five out of 30 patients with temporal lobe epilepsy as having normal hippocampal MRI features. Our method of combining quantification and distribution graphs of HT2 and HV found unilateral focal HT2 abnormalities without any volume loss in three of these five patients on the side identified as the seizure onset. In three of the 30 patients with temporal lobe epilepsy, HT2 measurements were normal on the central slice showing the brainstem (as used in previous studies⁵), but were abnormal anteriorly, accompanied by an anterior volume loss in one case and normal HV_c in two cases.

In two of four patients diagnosed as having bilateral hippocampal sclerosis by visual inspection, we confirmed these findings by quantification. In the remaining two patients with visually judged bilateral hippocampal sclerosis, we identified quantitative abnormalities typical of hippocampal sclerosis on one side only. The HV and HT2 distribution graphs showed these hippocampi to be unilaterally and diffusely affected.

Six patients had bilateral hippocampal involvement on quantitative MRI, all with bilateral abnormally high HT2 but unilateral or bilateral volumetric abnormalities. Analysis of HT2 and HV profiles showed two patients with bilateral diffuse HT2 changes to have unilateral HV loss (fig 5) on the side which was concordant with the electrophysiological seizure onset. One of these has had surgery so far and hippocampal sclerosis was confirmed on histology. The four remaining bilaterally abnormal patients with temporal lobe epilepsy were affected on MRI quantification in varying degrees. In two of these cases, there were diffuse HT2 and HV abnormalities on the side of seizure onset and focal MRI changes on the other. In one of them, the side which was diffusely affected on MRI quantification was operated on, with pathological confirmation of hippocampal sclerosis. The last two patients had bilateral asymmetric abnormal quantitative MRI features without electrophysiological lateralisation.

PATIENTS WITH EXTRATEMPORAL EPILEPSY

Nine of 10 patients with extratemporal seizures showed no hippocampal abnormality. One patient with Sturge-Weber syndrome had bor-

derline small HV_c, anteriorly high HT2, and cerebral hemiatrophy on the same side as the extratemporal angiomas.

GROUP ANALYSIS

In controls, HT2 values were higher anteriorly than posteriorly (table 1). In patients with temporal lobe epilepsy with diffusely affected hippocampi, HT2 values were higher anteriorly than posteriorly ($n=28$, $p<0.001$). The mean posterior-anterior gradient of HT2 was steeper in diffuse hippocampal sclerosis (mean 1.66 (SD 1.9) ms/slice position), than in controls (mean 0.48 (SD 0.61) ms/slice position) ($p<0.001$).

CLINICAL CORRELATIONS

The patient groups and control subjects did not differ in age. Duration of epilepsy did not differ between the temporal lobe epilepsy patient groups (table 2). The age of onset of epilepsy was least in the group with bilateral hippocampal sclerosis, followed by the unilateral diffuse and the unilateral focal groups, whereas the two patients with normal MRI were obviously older at the age of onset ($p=0.05$). There were no significant differences in frequency of a history of complicated febrile convulsions. Five of 16 patients with MRI features of unilateral diffuse hippocampal sclerosis (31%) and none of the other patients with temporal lobe epilepsy had a history of meningitis or encephalitis ($p=0.04$). All six patients with MRI features of bilateral hippocampal sclerosis had more than 10 secondarily generalised tonic clonic seizures in their lifetime, while 11 of the remaining 24 patients with temporal lobe epilepsy (46%) had more than 10 ($p=0.02$). There were no significant differences in the complex partial seizures frequencies between the groups of patients with temporal lobe epilepsy.

There were no significant differences between patients with temporal and with extratemporal seizure onset for age at time of study, age of onset, duration, frequency of meningitis or encephalitis, seizure frequency, or the occurrence of more than 10 secondarily generalised tonic clonic seizures in life.

Discussion

In this study we have shown that measurements of HT2 along the length of the hippocampus are complementary to measures of HV, and refine the presurgical assessment of patients with temporal lobe epilepsy²² and the definition

of the range of hippocampal sclerosis.⁴ Quantification identified more patients with hippocampal abnormalities than did qualitative evaluation. In three out of five patients in whom the hippocampi were regarded as normal on qualitative assessment, quantification identified focal abnormalities of HT2. The presurgical identification of hippocampal sclerosis by quantitative techniques is important for patients with mild or bilateral atrophy which are difficult to distinguish from normal findings.^{10 11 23}

METHODOLOGICAL ISSUES

Our method of measuring contiguous multislice HT2 was rapid, easy to implement on a standard clinical MRI system, reliable, and utilised data acquired for routine proton density and T2 weighted imaging.¹³ The sequences used are available on any contemporary clinical MR scanner and the technique is easy to adopt. However, it has to be stressed that reproducibility and stability studies are necessary before establishing a normal range for each MR scanner, and before attempting to distinguish normal from abnormal hippocampi using T2 relaxometry, as shown earlier for our site.¹³

Previously HT2 has only been measured on one or on few thick slices with interslice gaps^{4 12 14-16} and so were prone to miss localised changes. We found increased sensitivity measuring HT2 throughout the hippocampus. Three patients had abnormal anterior HT2 on the side of electrophysiological seizure onset, although the HT2 on the slice showing the brainstem (as used in a previous study⁴) were normal. In one case, this was accompanied by a focal anterior hippocampal volume loss. Values for HT2 and volumetric data corresponded in most of the cases, although HT2 measurements throughout the hippocampus added more evident information about the extent of MRI features of hippocampal sclerosis than volumetric measurements in 10 out of 30 patients with temporal lobe epilepsy, whereas volumetric measurements showed more evident abnormalities in four of the patients.

Our volumetric/morphometric data and HT2 measurements were aligned and topographical agreement between the two measurements achieved by measuring both parameters in the same orientation using the same internal hippocampal landmarks. The length of the right and left hippocampus varied by up to 6 mm in five of our 20 control subjects. Measurements at a given slice position intersected slightly different portions of the left and right hippocampus. To minimise these problems it was important to avoid asymmetries due to rotation of the head during data acquisition. These variations contributed to the spread of control HT2 values and therefore to the established normal ranges along the length of the hippocampus. Values for each slice position were judged against the normal range of HT2 at that distance anterior from the slice in which the fornix was seen in its maximum extent. These limitations have even greater effect on studies using just one single or a few slices to measure HT2.^{4 12 14-16}

Small encystments of the hippocampal or uncus sulcus with the same signal intensity as CSF which might contribute to higher HT2, were found in controls and patients, but were easy to avoid when measuring HT2.²⁴ Potential CSF signal contamination from other sources were also minimised by careful placement of the regions of interest.

Values for HT2 were significantly higher in the anterior than the posterior hippocampus in control subjects. This tendency was also found in a recent study, but was not significant, probably due to the larger ranges in that investigation.¹⁵ The topographical variation of HT2 throughout the hippocampus of controls represents changes in the MRI detectable structure of the hippocampus and are not a systematic slice to slice variation generated by our pulse sequence as our slices were acquired in a multislice interleaved fashion. Neuronal densities also vary throughout the normal hippocampus, being lower in the anterior than the posterior part.^{2 25 26} This antero-posterior gradient is even more marked in hippocampal sclerosis, with neuronal loss being generally more severe anteriorly,^{25 26} and is reflected in the markedly higher HT2 anteriorly in patients with apparently diffuse hippocampal sclerosis. The ratio of glial cell densities and neuronal cell densities in the hippocampal subfield CA 1 is an important determinant of quantitative MRI changes in hippocampal sclerosis.²⁷ Neuronal loss underlies atrophy and may also participate in the increase of HT2. Grey matter, which is rich in neurons, has a lower T2 value than white matter or gliosis.²⁸ Increases in HT2 and apparent diffusion coefficient (ADC) maps suggest that more free water, associated with relative expansion of extracellular space secondary to loss of neurons, contributes to higher HT2.²⁹

RANGE OF HIPPOCAMPAL SCLEROSIS IDENTIFIED

The anterior part of the hippocampus was most commonly affected by hippocampal sclerosis and in diffuse hippocampal sclerosis, there is evidence from HT2 studies of more severe damage anteriorly. We also identified MRI negative, bilateral small, and unilateral small hippocampi with a predominance of diffuse or anterior involvement. No unilateral posterior focal volume loss^{3 30} or focal posterior high HT2 was found. Previous reports on the patterns of hippocampal sclerosis seen on MRI have described diffuse hippocampal sclerosis with an anterior predominance,^{4 31} focal hippocampal sclerosis affecting the body of the hippocampus,^{30 32} and focal anterior hippocampal sclerosis.^{3 33} We found diffuse involvement in 73% of unilateral cases, and focal anterior hippocampal sclerosis in 27%. The relative incidence of unilateral focal/anterior *v* unilateral diffuse MRI features of hippocampal sclerosis of 1: 2.7 compares with 1: 0.5-1: 8.2 in other series,^{3 4 32} most likely reflecting differences in study design, patient selection, and methods.

Our method detected bilateral hippocampal abnormalities in 20% of medically refractory patients with temporal lobe epilepsy referred

for presurgical evaluation, compared with a range from 8% to 46% in previous studies using HT2 or volumetric measurements.^{4 11 12 14 34 35}

CLINICAL CORRELATIONS

The number of patients used necessitates caution in interpreting clinical correlations. Patients with bilateral hippocampal sclerosis had a younger age of onset of epilepsy than patients with unilateral sclerosis and all patients with bilateral hippocampal sclerosis had more than 10 secondarily generalised tonic clonic seizures, similar to other reports.⁴ The question of whether bilateral hippocampal sclerosis is the cause or consequence of recurrent secondarily generalised tonic clonic seizures early in life can only be answered by a prospective longitudinal study of many patients, from the onset of their epilepsy. Similar considerations apply to the extent of unilateral hippocampal sclerosis. The age of onset of epilepsy was lower in the unilateral diffuse than in the unilateral focal group, and the proportion of patients with more than 10 secondarily generalised tonic clonic seizures during their lifetime was higher in the unilateral diffuse group.

Febrile convulsions did not correlate with any one pattern of hippocampal sclerosis. All patients with a history of meningitis or encephalitis had MRI features of unilateral diffuse hippocampal sclerosis. Previous studies of patients with temporal lobe epilepsy have found a history of meningitis or encephalitis to be associated with unilateral hippocampal sclerosis,³⁶ bilateral hippocampal atrophy,¹¹ and have not shown an association with one pattern.⁴ These interstudy differences are most likely due to differences in patient selection and MRI methodology, and whether qualitative³⁶ or quantitative methods were used.

IMPLICATIONS FOR PRESURGICAL EVALUATION

Quantitative MRI of hippocampi is a key part of the assessment of patients with partial seizures and is complementary to seizure semiology, EEG, and psychometry. In our study, two out of 30 medically refractory patients with temporal lobe epilepsy referred for presurgical evaluation were MRI negative and in the extratemporal group we identified one patient (10%) with MRI features of hippocampal sclerosis—that is, dual pathology. It must be emphasised that MRI cannot distinguish the epileptogenic from the non-epileptogenic lesion.³⁷ In patients with bilateral MRI abnormalities, hippocampal sclerosis may be present on the side that does not give rise to seizures,²³ but contributes to neuropsychological impairment.³⁸

The combination of HT2 and volumetric measurements and morphometric analysis is sensitive to subtle and localised changes, which may otherwise be missed. These data also suggest the possible utility of undertaking tailored resections of the hippocampus, with sparing of normal hippocampal tissue.

These methods are also appropriate for longitudinal and prognostic studies. Patients with temporal lobe epilepsy with hippocampal scler-

osis are at a higher risk for late seizure recurrence 30–60 months after surgery compared with patients with foreign tissue lesions detectable by MRI.²² In this respect the postero-anterior extent of hippocampal sclerosis may be a predictor. In a histopathological study, patients with diffuse hippocampal sclerosis had a worse surgical outcome than those with focal anterior neuronal loss.² Sparing of the posterior portion of the hippocampus did not relate to the outcome after anterior temporal lobe resection in a study of patients with unilateral diffuse hippocampal sclerosis.³¹ We are currently undertaking a prospective study to determine the prognostic relevance of HT2 and HV data in patients with hippocampal sclerosis having anterior temporal lobe resections.

In conclusion, measurement of regional abnormalities of HT2 along the length of the hippocampus is not time consuming, provides further detail in the MRI assessment of the hippocampus, and supplements volumetric and morphological data in the evaluation of patients with temporal lobe epilepsy.

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