Quantitative MRI in patients with idiopathic generalized epilepsy
Evidence of widespread cerebral structural changes

F. G. Woermann[1], S. M. Sisodiya[1,2], S. L. Free[1] and J. S. Duncan[1]

[1]*The MRI Unit, National Society of Epilepsy and Epilepsy Research Group, University Department of Clinical Neurology, Institute of Neurology, London and* [2]*Department of Neurology, Radcliffe Infirmary, Oxford, UK*

Correspondence to: Professor J. S. Duncan, National Society for Epilepsy, National Hospital for Neurology and Neurosurgery, Chalfont St Peter, Gerrards Cross, Bucks SL9 0RJ, UK

Summary

In patients with idiopathic generalized epilepsy (IGE), visual inspection of routine MRI is normal. However, pathological studies have shown microdysgenesis in grey and white matter in a large percentage of autopsies from cases of IGE. Recently, widespread structural changes not evident on visual inspection of high resolution MRI have been shown using quantitative MRI in patients with apparently focal cerebral dysgenesis. We sought to determine whether similar quantitative changes might be present in patients with IGE, reflecting possible underlying structural abnormalities. Twenty patients with juvenile myoclonic epilepsy, 10 patients each with childhood absence epilepsy and juvenile absence epilepsy, five patients with tonic–clonic seizures on awakening and 30 control subjects had T_1-weighted volume acquisition MRI scans on a 1.5T GE scanner. The cerebral hemi-spheres were segmented semi-automatically, allowing the comparison of normalized cortical and subcortical matter volumes between groups, and investigation of the regional distribution of cortical and subcortical matter in individual subjects. Patients with IGE had significantly larger cortical grey matter volumes than control subjects. Significant abnormalities of the regional distribution of cerebral grey and subcortical matter were found in eight out of 20 patients with juvenile myoclonic epilepsy, one out of 10 patients with childhood absence epilepsy, four out of 10 patients with juvenile absence epilepsy and two out of five patients with tonic–clonic seizures on awakening, but in none of the 30 control subjects. Using MRI-segmentation, we identified widespread cerebral structural changes in patients with various IGE syndromes. Quantitative MRI supports the existence of structural abnormalities in patients with IGE.

Keywords: idiopathic generalized epilepsy; MRI; morphometry

Abbreviation: IGE = idiopathic generalized epilepsy

Introduction

Idiopathic generalized epilepsy (IGE) is characterized by the clinical triad of typical absences, tonic–clonic seizures and myoclonic jerks. The various IGE syndromes are defined by these seizure types and by their electrophysiological features indicating involvement of both cerebral hemispheres from the very beginning of the seizure; they differ mainly in their age of onset.

The 1985 International League Against Epilepsy definition of idiopathic generalized epilepsies contains the term 'no neuroradiological signs' in these patients (Commission on Classification, 1985). Visual inspection of routine high reso-lution MRI is normal in patients with IGE. Recently, func-tional imaging has shown various abnormalities in patients with IGE: increase of thalamic blood flow during absence seizures (Prevett *et al.*, 1995), altered benzodiazepine receptor density in cortex, thalamus and cerebellum (Savic *et al.*, 1994; Koepp *et al.*, 1997), and association between impaired visual working memory and altered [18F]fluorodeoxyglucose uptake in different cortical areas (Swartz *et al.*, 1996). These findings support the pathophysiological concept of functional abnormalities of the thalamocortical circuit in patients with IGE which has been derived from animal work and depth EEG studies (Williams, 1953; Velasco *et al.*, 1989; Gloor, 1995).

Pathological studies of patients with IGE are very rare. However, the autopsy studies of Janz and Meencke (Janz and Neimanis, 1961; Meencke and Janz, 1984; Meencke, 1985) have shown cortical and subcortical dystopic neurons and other microscopic structural abnormalities ('microdys-genesis') in a large percentage of a small number of cases with IGE. The significance of these findings, however, is

Table 1 *Demographic and clinical features of all patients with IGE and for the various subgroups*

Syndrome	Idiopathic generalized epilepsy ($n = 45$)	Juvenile myoclonic epilepsy ($n = 20$)	Childhood absence epilepsy ($n = 10$)	Juvenile absence epilepsy ($n = 10$)	Tonic clonic seizures on awakening ($n = 5$)
Gender (female/male)	25/20	12/8	7/3	5/5	1/4
Age: mean and range (years)	24.5 (14–39)	24.8 (15–37)	24.3 (14–36)	24.5 (16–39)	23.8 (21–28)
Age at onset: mean and range (years)	12.2 (1–21)	14.3 (7–21)	6 (1–9)	13.1 (10–19)	14.8 (8–18)
Duration: mean and range (years)	12.3 (1–31)	10.5 (1–28)	18.3 (8–31)	11.4 (3–29)	9 (5–14)
Numbers of patients with					
absences	30 (67%)	9 (45%)	10 (100%)	10 (100%)	1 (20%)
myoclonic jerks	25 (56%)	20 (100%)	3 (30%)	1 (10%)	1 (20%)
generalized tonic clonic seizures	40 (89%)	20 (100%)	6 (60%)	9 (90%)	5 (100%)
>10 generalized tonic clonic seizures	19 (42%)	6 (30%)	6 (60%)	5 (50%)	2 (40%)
inducible EEG changes*	13 (29%)	6 (30%)	2 (20%)	3 (30%)	2 (40%)
family history of epilepsy	16 (36%)	7 (35%)	2 (20%)	3 (30%)	4 (80%)
remission of epilepsy	20 (44%)	12 (60%)	3 (30%)	2 (20%)	3 (60%)

*Epileptiform activity inducible by photostimulation or hyperventilation.

controversial (Lyon and Gastaut, 1985). It is possible, therefore, that patients with clinically typical IGE may have structural cerebral abnormalities. Such abnormalities associated with epilepsy may be subtle and not visualized macroscopically on MRI, at surgery (Palmini *et al.*, 1995) or at post-mortem (Ferrer *et al.*, 1992).

In patients with apparently focal cerebral dysgenesis, however, widespread structural cerebral changes not visible on high-resolution MRI were demonstrated beyond the margins of the visualized lesion using MRI quantification with a method based on measurements of cortical and subcortical matter in specified volumes of interest (Sisodiya *et al.*, 1995). Similar widespread extratemporal structural changes were also correlated with an unfavourable outcome after anterior temporal lobe resections in patients with temporal lobe epilepsy and hippocampal sclerosis, thus connecting these volumetric findings with epileptogenicity (Sisodiya *et al.*, 1997). We have applied the same quantitative MRI method to patients with IGE to determine whether subtle structural abnormalities might also be demonstrated in these patients.

Method
Subjects
After the ethical committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology approved our study, and after individual informed consent was obtained, we studied 45 patients (25 women and 20 men; mean age 24.5 years, with median age 24 years and range 14–39 years). These comprised 20 patients with juvenile myoclonic epilepsy, 10 patients each with childhood absence epilepsy and juvenile absence epilepsy, and five patients with tonic–clonic seizures on awakening. The patients had been referred to the Epilepsy Centre of the National Hospital for Neurology and Neurosurgery, London, and clinically evaluated by a consultant neurologist (J.S.D.). Demographic and clinical features are summarized in Table 1; 27 patients

were treated with anti-epileptic drug monotherapy, 14 with polytherapy and four were untreated at the time of scanning. We also studied 30 control subjects (16 women and 14 men; mean age 24.5 years, with median age 27 years and range 14–36 years) who had no history of neurological or psychiatric disease. There was no age difference between the different patient groups and the control subjects.

MRI
MRI was performed on all subjects according to the same protocol, using a 1.5T GE Signa scanner (Milwaukee, Wisc., USA). An inversion recovery-prepared 3D spoiled gradient echo (IRP-SPGR) sequence (TR/TE/TI 17.4/4.2/450 ms, flip angle 20, matrix size 256 × 192 and field of view 24 × 18 cm) with 124 contiguous coronal slices and a slice thickness of 1.5 mm was used for volumetric studies. All MRIs were reviewed by experienced neuroradiologists and reported as normal.

Segmentation of MRI and MRI volumetry
MRIs were transferred to an independent image-analysis workstation (Allegro, ISG Technologies, Toronto, Canada), allowing the semi-automated selection of defined regions of interest from the contiguous coronal images. This segmentation technique employed interactive thresholding of signal intensity between grey matter and CSF, and between grey and white matter, and utilized an automated seed growing algorithm. The method quantified the amounts of cortical grey matter and subcortical matter (white matter and basal nuclei excluding the caudate) using region-of-interest boundaries, as previously published (Sisodiya *et al.*, 1995). The 2D regions of interest containing grey or subcortical matter were used for the reconstruction of 3D images of cortical and subcortical matter, and for subsequent volume measurements as described previously (Sisodiya *et al.*, 1995).
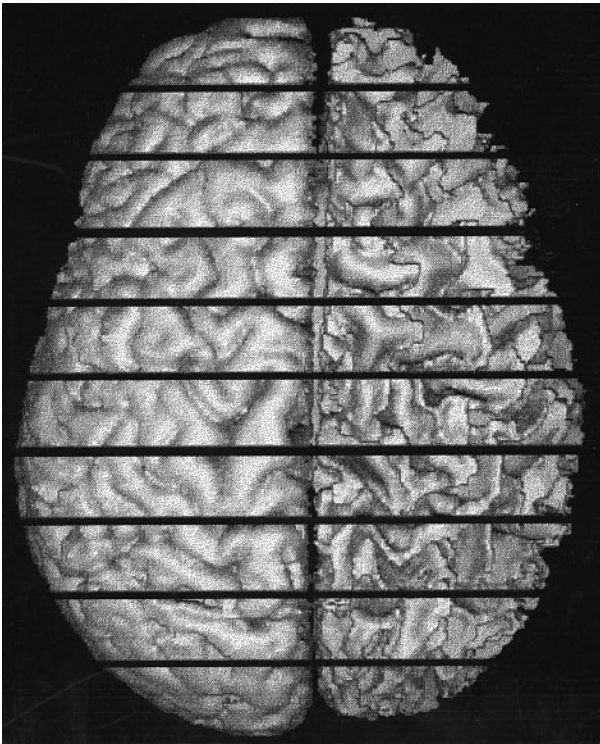
Fig. 1 Three-dimensional reconstruction of control grey (left of image) and subcortical matter (right of image) with volumes of interest representing tenths of the anterior–posterior extent of the cerebrum. Each volume of interest was described by a number of values: normalized volumes of grey matter and subcortical matter, the ratio of ipsilateral grey to subcortical matter, the ratios of left- to right-sided grey matter and left- to right-sided subcortical matter.

In detail, cortical grey and subcortical matter were reconstructed as total volumes as well as within prescribed proportions or volumes of interest within each individual hemisphere (Fig. 1). Each volume of interest covered one-tenth of the anterior–posterior axis of the hemisphere. The grey and subcortical volumes from each hemisphere and each volume of interest were corrected ('normalized') for the individual's brain size by dividing each measure by the total measured cerebral volume, thus expressing volumes as percentages of the cerebral volume and allowing comparison between subjects and groups. Ratios of ipsilateral cortical to subcortical matter in volumes of interest and ratios of ipsi- to contralateral volumes of homologous volumes of interest were also calculated. Thus, 80 volume-of-interest variables per subject described MRI-detectable brain structures quantitatively and with regional specificity. We defined a normal range for each of these 80 values from our data on 30 control subjects. The normal range was defined as that within 3 SD of the mean.

In a previous study, a high degree of intra- and inter-observer reliability for this method was established (Sisodiya *et al.*, 1995). With images of control subjects and patients randomly intermixed, all the images of our study were segmented by one operator (F.G.W.) who was blinded to whether or not a particular dataset was from a patient or a control subject and who had an intrarater coefficient of repeatability of 6%, established in cortical volumes from repeated measurements of five control subjects (Bland and Altmann, 1986).

Statistics

For all the measurements and derived values of the control group ($n = 30$), the normality of the distribution was tested using the Kolmogorov–Smirnov goodness-of-fit test, before establishing normal ranges consisting of the control mean ± 3 SD. The sample size differed between control subjects and patients; in patient subgroups, $n \leqslant 30$; the same applied for comparisons between gender subgroups. Therefore, central tendencies were tested using the Mann–Whitney U test and the Kruskal–Wallis ANOVA. Categorical data were tested for association using Fisher's exact test. Analysis was carried out using SPSS 6.1 for Windows.

Results

In control subjects, the mean total cerebral volume ($\pm$ SD) was 1017 ± 128 cm^3. There was a gender related difference in overall cerebral volume. The mean female cerebral volume ($n = 16$) was 961 ± 96 cm^3, while the mean male cerebral volume ($n = 14$) was 1081 ± 134 cm^3 (Mann–Whitney U test, $P = 0.007$). There was no age related difference of overall cerebral volume in the control group.

The normalized cortical grey matter was calculated as a ratio of absolute cortical volume divided by the total cerebral volume; its mean value in control subjects ($\pm$ SD) was $58.2 \pm 2.4\%$. The subcortical matter volume had a mean proportion of $41.8 \pm 2.4\%$ of the total cerebral volume in control subjects. There was no gender difference after normalization of cortical and subcortical matter volumes.

For the regional measurements, three normal subjects had only one of 80 volume-of-interest values per subject outside the normal range (mean $\pm$ 3 SD), each of these variables being normally distributed. The other 27 had no abnormal values. On this basis, the presence of two or more abnormal values per single subject was used to define a structurally abnormal brain, as described previously (Sisodiya *et al.*, 1995, 1997).

In 45 IGE patients, the mean total cerebral volume ($\pm$ SD) was 984 ± 109 cm^3. The mean cerebral volume in female patients ($n = 25$) was 943 ± 100 cm^3, which was significantly less than the mean male cerebral volume ($n = 20$) of 1037 ± 101 cm^3 (Mann–Whitney U test, $P = 0.008$). There was no difference in mean total cerebral volume between female control subjects and female IGE patients (Mann–Whitney U test, $P = 0.29$) or between male control subjects and male IGE patients (Mann–Whitney U test, $P = 0.15$).

In the patients with IGE, the mean normalized cortical matter ($\pm$ SD) was $60.6 \pm 2.6\%$, which was significantly

greater than in the control data (58.2 ± 2.4%), (Mann–Whitney U test, $P < 0.001$) (Fig. 2). The subcortical matter, with a mean proportion of 39.4 ± 2.6% of the total cerebral volume, was significantly less than the control mean (41.8 ± 2.4%) (Mann–Whitney U test, $P < 0.001$). Comparing control subjects with the different groups of IGE syndromes, these differences were confirmed; there were differences between control subjects and patients of different subgroups with IGE in mean cortical and subcortical matter volumes (Kruskal–Wallis ANOVA, $P < 0.001$) (Fig. 2).

Comparing individual values of whole brain cortical or subcortical matter with the established normal range consisting of the control mean ± 3 SD, one juvenile myoclonic epilepsy patient out of the 45 patients with IGE (2.2%) had an abnormally high normalized cortical volume and an abnormally low subcortical volume.

In 45 patients with IGE, significant regional quantitative abnormalities of cerebral structure (defined as more than one abnormal volume-of-interest value out of 80 values per person) were found in 15 out of these 45 (33%). In detail, eight out of 20 patients with juvenile myoclonic epilepsy, four out of 10 with juvenile absence epilepsy, one out of 10 patients with childhood absence epilepsy and two out of five with tonic–clonic seizures on awakening had a significant abnormality of cerebral structure.

In those patients with significant regional abnormalities of cerebral structure, there were 81 abnormal volume-of-interest values in total. The mean number of abnormal volume-of-interest values was 5.4 per patient with significant regional abnormalities of cerebral structure; the corresponding range was 2–14 per patient.

In the 15 patients with significant abnormalities of cerebral structure as defined above, the majority of the abnormal values were found within the central volumes of interest of the affected brains without any more precise localization. Forty abnormal ratios of ipsilateral cortical to subcortical matter volumes were identified, of which all had values greater than the normal range and 21 were describing left-sided volume of interest, while 19 abnormal ipsilateral ratios were found in the right hemisphere.

In the overall IGE group, there was no correlation between a significant abnormality of cerebral structure and age at scan, age of onset, duration of epilepsy, the incidence of >10 generalized tonic–clonic seizures in life, a family history of epilepsy or whether the patient had been seizure free or not for >1 year at the time of the investigation. Five out of eight patients with juvenile myoclonic epilepsy and significant structural abnormalities had a family history of epilepsy (there were data missing on a family history in one juvenile myoclonic epilepsy patient with structural abnormalities). In contrast, only two out of 10 juvenile myoclonic epilepsy patients without structural abnormalities had a positive family history (Fisher's Exact Test, $P = 0.045$).

Discussion

We have demonstrated subtle widespread cerebral structural changes in patients with IGE, using MRI volumetry.
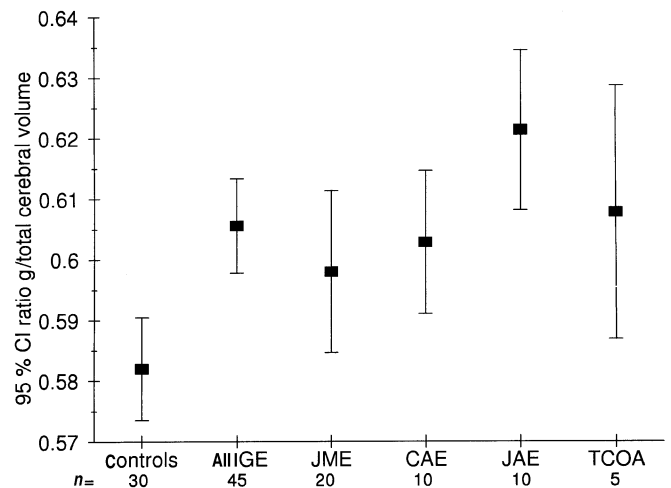

Fig. 2 Mean normalized grey matter volumes (grey matter : total cerebral volume) (filled squares) in the control group, for all patients with idiopathic generalized epilepsy (IGE) and for the subsyndromes. JME = juvenile myoclonic epilepsy; CAE = childhood absence epilepsy; JAE = juvenile absence epilepsy; TCOA = tonic–clonic seizures on awakening. The bars indicate the 95% confidence interval.

The mean values for total cortical and subcortical matter, normalized as ratios of the overall cerebral volume, differed between 30 normal subjects and 45 IGE patients, pointing to a possible widespread abnormality of the overall grey and white matter in patients with IGE. Comparing all the different subsyndromes, this difference in mean volumes was most marked between 30 normal subjects and 10 juvenile absence epilepsy patients (Fig. 2). Analysis of individual patients showed the normalized MRI volumes of total cortical and subcortical matter to be abnormal in only one out of 45 IGE patients. A rate of 2.2% of all IGE patients with abnormally high grey and abnormally low subcortical matter lies just outside what one would expect as a finding by chance. The volume-of-interest approach identifies localized abnormalities on a smaller scale which might affect values in just one hemisphere. Thirty-three per cent of 45 IGE patients showed these volume-of-interest-based abnormalities of cerebral structure. Thus, differences of both mean values of cortical and subcortical matter volumes, and differences comparing volumes of interest between individual patients and with the control range, support the existence of structural cerebral abnormalities in some patients with IGE.

We have previously postulated that structural changes detected on MRI quantification are possibly due to changes in neuronal connectivity (Sisodiya *et al.*, 1995). The basic tenet is that neocortical grey matter volumes allow inferences to be drawn about the number of cellular elements in these structures, especially those contributing to the neuropil (Caviness *et al.*, 1996). This technique was subsequently used to demonstrate widespread structural abnormalities in patients with epilepsy and hippocampal sclerosis who had persistent seizures after temporal lobectomy (Sisodiya *et al.*,

1997). These findings have shown that, in patients with hippocampal sclerosis at least, the structural changes detected by MR quantification are biologically relevant, being associated with epileptogenicity.

In our group of 15 IGE patients with significant abnormalities of cerebral structure, there were 81 abnormal volume-of-interest values. As in previous studies, all 40 abnormal ratios of ipsilateral cortical volume over the subcortical matter volume were increases above the upper limit of the normal range (Sisodiya *et al.*, 1995). Increases in grey matter to subcortical volume ratios might be due to an increase in the number or volume of neurons or neuropil in the grey matter, or to a decrease of the white matter in the same volume of interest. It is possible that an increased number of neurons project axons of reduced volume into the underlying subcortical matter. A loss of volume of the subcortical matter might be the consequence of axons which are thinner and have an altered terminal arborization and connectivity (Mitchison, 1991). An increase in the cortical : subcortical volume ratio might also be the consequence of more axons failing to enter the subcortical matter at all, as described previously in patients with malformations of cortical development (Takada *et al.*, 1988; Ferrer *et al.*, 1992). All these possibilities suggest altered interneuronal connectivity as a possible histological implication of our findings of structural cerebral abnormalities in patients with IGE.

It is not known, however, whether similar quantitative MRI abnormalities in patients with partial seizures and malformations of cortical development and in patients with IGE are due to the same specific anatomical structural changes. Pathological studies are needed to address this question and these are very rare in patients with IGE. Autopsy studies that have been performed in a small number of patients with IGE have shown dystopic neurons in the grey and white matter and other abnormalities (so called 'microdysgenesis') in patients with IGE (Janz and Neimanis, 1961; Meencke and Janz, 1984; Meencke, 1985). Structural abnormalities such as 'microdysgenesis' could explain changes in the volume of interest by increasing the volume of the grey matter ribbon. However, these pathological studies only involved a small number of brains, and they did not study volumetric features in patients with IGE so direct comparison with our study is limited. Additionally, the definition of 'microdysgenesis' and its meaning in patients with IGE have been controversial (Lyon and Gastaut, 1985). Given the possible diffuse and synaptic nature of changes in patients with IGE, histopathological proof, especially of connectivity changes in humans, may not be feasible (Huttenlocher, 1974). Further quantitative MRI as a surrogate for histology might be the only method to examine the whole cortical and subcortical matter and connectivity in adequate detail *in vivo* (Sisodiya and Free, 1997), but it would be strengthened by correlation of MRI studies and pathology in future case studies.

Our findings of quantitative MRI abnormalities in IGE

might also be the structural correlate of functional abnormalities in patients with IGE shown recently by functional imaging (Savic *et al.*, 1994; Swartz *et al.*, 1996; Koepp *et al.*, 1997). PET studies have shown increases of cortical and thalamic blood flow during absence seizures (Prevett *et al.*, 1995). It would be of interest to segment the thalamus as a volume of interest to detect morphological changes. This was not possible in the current study as presently available T_1-weighted volume acquisition MRI are not suitable for the segmentation of the thalamus. There is a single patient with IGE in the literature who at autopsy had morphological abnormalities in the thalamus which, at the time, were judged to be residues of ischaemic neuronal damage (Meencke and Janz, 1984).

The main pathophysiological concept in IGE invokes functional abnormalities of the thalamocortical circuit. Although two depth EEG studies in humans with IGE found discharges starting in the thalamus before those in the cortex (Williams, 1953; Velasco *et al.*, 1989), animal data and clinical studies in patients with IGE support the view that cortical hyperexcitability is an important part of the pathophysiology of IGE (Gloor, 1995; Niedermeyer, 1996). Our findings support the concept that structural cortical changes may be associated with abnormalities in functional connectivity within the cortex and, in some cases, between cortical and subcortical structures.

Not all of our patients with well-defined and homogeneous IGE syndromes had individually abnormal brains on MRI volumetry. Despite the homogeneity of the clinical syndromes, we cannot exclude underlying structural heterogeneity within these IGE subgroups. The result of regional quantitative abnormalities in a third of individual IGE patients may also be the consequence of a shift in the distribution of volumetric measurements in IGE resulting in the increase of cortical grey matter and decrease of subcortical matter in the IGE group compared with control subjects. Our volume-of-interest analysis used reproducible, but arbitrary volumes of interest in which large areas of normality might have swamped smaller areas of abnormality, thus reducing the sensitivity. The sensitivity of our method was also reduced by defining the normal range as the control mean $\pm$ 3 SD. However, this normal range was chosen deliberately, to reduce false positive results and to encompass normal variability.

In the overall IGE group no pertinent clinical features were associated with the existence of significant structural abnormalities on MRI quantification. Almost all patients were treated with anti-epileptic drugs. None had suffered from a drug-related encephalopathy. A relatively low percentage of our patients were in remission, possibly as a consequence of bias introduced into our study by patient recruitment at a tertiary referral centre for adult patients with epilepsy. The incidence of remission was not correlated with the lack of structural abnormalities detected by MRI quantification. Previous MRI studies have shown that significant structural abnormalities were not an epiphenomenon of seizures, their treatment and their other consequences; a group of patients

with refractory temporal lobe epilepsy and hippocampal sclerosis did not show widespread structural changes, thus demonstrating methodological specificity (Sisodiya *et al.*, 1997).

In juvenile myoclonic epilepsy patients with structural abnormalities, the proportion of patients with a positive family history was larger than in the subgroup without structural abnormalities. Although the statistical significance of this finding has to be judged carefully, it is of interest. There is a strong genetic component in the pathophysiology of IGE, as indicated by twin and genetic studies (Berkovic *et al.*, 1994; Serratosa *et al.*, 1996, Elmslie *et al.*, 1997). MRI quantification of grey and white matter volumes in large pedigrees of patients with IGE might contribute to the description and distinction of different phenotypes in patients with IGE, and aid genetic analysis.

In conclusion, this is the first *in vivo* imaging demonstration of subtle, but widespread, cerebral structural changes in subgroups of patients with various IGE syndromes, using interactive MRI segmentation.

Acknowledgements

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