Magnetic resonance imaging findings within 5 days of status epilepticus in childhood

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Summary
The nature of the relationships between status epilepticus, acute hippocampal injury, mesial temporal sclerosis (MTS) and temporal lobe epilepsy remains unclear. The aim of this study was to investigate whether generalized status epilepticus is associated with brain abnormalities, especially in the mesial temporal lobe, within 5 days of the acute event. Such changes may be the first part of a causative pathophysiological sequence relating status epilepticus and MTS. Thirty-five children with a history of status epilepticus, including 21 with a history of prolonged febrile convulsion (PFC), underwent qualitative and quantitative MRI investigations within 5 days of the acute episode. Quantitative assessments of the hippocampus included T2 relaxometry and hippocampal volumetry. Hippocampal volumes were large in patients with PFC when compared with controls. In addition, T2 relaxation time was elevated in patients with PFC compared with control subjects during the first 2 days of the acute event. No difference was observed in patients examined 3–5 days after the event. Patients with afebrile status epilepticus had a variety of imaging abnormalities including elevated hippocampal T2 values, but no evidence of hippocampal enlargement. PFC is associated with hippocampal abnormalities, consistent with hippocampal oedema, whilst non-febrile status epilepticus is not. A systematic longitudinal study is required to characterize the evolution of these abnormalities and to determine whether any patient develops MTS.

Keywords: hippocampal volume; MRI; prolonged febrile convulsion; status epilepticus; T2 relaxometry

Abbreviations: ASE = afebrile status epilepticus; HCV = hippocampal volume; ICV = intracranial volume, IQR = interquartile range; MTS = mesial temporal sclerosis; PFC = prolonged febrile convulsion

Introduction
Status epilepticus is the most common medical neurological emergency in childhood and is associated with significant morbidity and mortality (Towne et al., 1994; DeLorenzo et al., 1996). There is continued debate on whether status epilepticus can cause acute hippocampal injury, which could evolve into mesial temporal sclerosis (MTS). Work in animal models suggests that limbic status epilepticus may result in neuronal injury, especially in the hippocampus, although other brain regions may also be injured (Shorvon, 1994). Many species and many experimental paradigms have been used in attempts to confirm a causative relationship. The hippocampal and mesial temporal lobe histological abnormalities following status epilepticus in animal models are similar across species and methods (Ben-Ari, 1985; Liu et al., 1994; Cavalheiro, 1995; Fountain and Lothman 1995; Golden et al., 1995; Fujikawa, 1996; Priel et al., 1996; Meldrum, 1997), suggesting that it is status epilepticus that results in hippocampal and temporal lobe injury rather than something directly related to any particular method of inducing status epilepticus.

In animal models of status epilepticus, MRI studies have demonstrated acute abnormalities in T2-weighted signal intensity, proton magnetic resonance spectroscopy (1H MRS) metabolite concentrations and ratios, and diffusion weighted images. In the kainic acid model, T2-weighted signal intensity has been shown to increase between 12 and 24 h after status epilepticus induction (Ebisu et al., 1996). Increased lactate signal on 1H MRI spectra from brain has been identified, and this increase correlates to the degree of histological damage (Ebisu et al., 1996; Najm et al., 1998). 1H MRS studies using N-acetylaspartate (NAA) as a marker of acute neuronal injury have produced less consistent results (Ebisu et al., 1994, 1996; Najm et al., 1998). Diffusion weighted
imaging acutely reveals a decrease in apparent diffusion coefficient, which may reflect underlying neuronal swelling (Zhong et al., 1993, 1995; Ebisu et al., 1996).

Termination of electrographic seizure activity results in a return of diffusion to normal within minutes of seizure termination (Zhong et al., 1995).

The most common association with MTS in humans is febrile convulsion in childhood (Cavanagh and Meyer 1956; Davies et al., 1996). When prolonged, febrile convulsions are a form of status epilepticus that, at least in some cases, is believed to have a genetic basis (Fukuyama et al., 1979; Annegers et al., 1982; Sunami et al., 1988; Tsuboi and Endo 1991). Febrile convulsions are common and affect ~3% of the population, although only a minority of these (5–10%) will be prolonged. Several thousand children annually will have a prolonged febrile convolution (PFC) and a proportion would be expected to develop MTS with symptomatic epilepsy. If there is a range of severity of damage resulting from febrile status epilepticus, MRI performed soon after the event may show asymptomatic abnormalities.

Some human MRI data on early brain abnormalities following status epilepticus have been reported. Hippocampal hyperintensity on qualitatively assessed scans has been identified on T2-weighted images following status epilepticus, with subsequent MRI-identified MTS reported in two out of 5 patients (Tien and Felsberg, 1995). Hippocampal asymmetry, consistent with hippocampal oedema, identified using hippocampal volume (HCV) measurements, has been reported in four out of 15 children following a prolonged and lateralized febrile convolution (VanLandingham et al., 1998). There is also some evidence that progression from normal hippocampus to MTS following status epilepticus can occur in children and adults (Nohria et al., 1994; Wiesmann et al., 1997).

Fig. 1 (A) Example slices from a reformatted 3D dataset. Five of a total of 45 images that were used in the calculation of hippocampal volumes are shown. The left is the most anterior, and the right the most posterior slice. (B) T2 map showing the positioning of a region of interest within the body of the left hippocampus.
The animal and human data outlined above suggest that status epilepticus may be associated with hippocampal abnormalities, which may represent the initial part of a causative pathophysiological sequence from status epilepticus to MTS. The aim of this study was to determine whether acute changes in the mesial temporal lobe are detectable using qualitative and quantitative MRI in patients undergoing investigation within 5 days of the acute event.

Methods
Patients were recruited from hospitals in the North Thames health region, London, and Great Ormond Street Hospital for Children NHS Trust. The study was approved by the hospital’s research ethics committee. Consent for enrolment into the study was given either by the parent of the child or by the child, with confirmation from the parent. Children within 5 days of an episode of status epilepticus (defined as a seizure or series of seizures lasting for ≥30 min, without return of consciousness between the seizures) were referred to the Neurology Unit at Great Ormond Street Hospital for further evaluation. On arrival at Great Ormond Street Hospital, each child was clinically assessed and data relating to pre-morbid state, precipitating factors, seizure onset and seizure length were obtained. Qualitative and quantitative MRI investigations were then performed under sedation or general anaesthesia, and were carried out within 5 days of the episode of status epilepticus. This study tested the hypothesis that patients with status epilepticus have evidence of brain abnormality within 5 days of the acute event.

Patients with a history of PFC (status epilepticus associated with a fever, not of CNS origin, occurring in developmentally normal children between the ages of 6 months and 5 years) were analysed separately from those with afebrile status epilepticus (ASE), as those in the former group are likely to be genetically distinct and the episode of status epilepticus is likely to occur within a narrow developmental window when compared with those with ASE. This separation is justified as MTS is more closely associated with febrile convulsion than ASE (Cavanagh and Meyer, 1956; Davies et al., 1996). As it is not ethical to sedate young children in order to obtain control data, a reference population was obtained from children undergoing scans for other reasons, e.g. skin lesions suggestive of neurocutaneous disorders, those undergoing staging of cancer and those with eye abnormalities. These children were all neurologically normal and had normal MRI on visual assessment.

The MRI investigations were carried out on either a Siemens (Erlangen, Germany) 1.5T SP whole body system (pre-1999) or a Siemens 1.5T Vision whole body system (post-1999). T1-weighted images were acquired using either a three-dimensional (3D) magnetization prepared rapid gradient echo (MPRAGE) sequence [repetition time (TR) = 10 ms; echo time (TE) = 4 ms; inversion time (TI) = 200 ms/NEX 1; flip angle 12°; matrix size 256 × 256; and 128 sagittal partitions in the third dimension with partition thickness of 1.25 mm] or a 3D fast low angle shot (3D FLASH) sequence (TR = 16.8 ms; TE = 5.7 ms/NEX 1; flip angle 21°, matrix size 200 × 256; and 160 partitions in the third dimension with a partition thickness of 1 mm). The data were reformatted into contiguous axial and coronal images. T2-weighted images (TE = 90 ms; TR = 4600 ms) were obtained in the coronal plane at 90° to the long axis of the hippocampus, and also in the tilted axial plane orthogonal to this. The images were reviewed by two neuroradiologists who were unaware of the clinical details, with emphasis on identification of abnormalities in the hippocampi and temporal lobes. However, abnormalities outside the hippocampi and temporal lobes were also sought.

Hippocampal volumetry was performed using the images obtained from the MPRAGE or FLASH sequences. The dataset was transferred to a personal computer and analysed using MEDx version 3.3 (Sensor Systems Inc., VA, USA). The data were reformatted in the tilted coronal plane, which was perpendicular to the long axis of the hippocampus. Each hippocampal slice was then measured (Fig. 1A). A 3D contour was derived from which the hippocampal volume was calculated. For the measurement of intracranial volume, the dataset was reformatted in the sagittal plane. The first slice was randomly selected, after which every fifth slice was systematically measured using landmarks described previously (Van Paesschen et al., 1997). A 3D contour was derived and the volume was calculated.

Hippocampal T2 maps were calculated from 16 images obtained with echo times ranging from 22–262 ms using a modified Carr–Purcell–Meiboom–Gill sequence, as described previously (Grünewald et al., 1994). The map was calculated by fitting a single exponential to the signal from each of the 16 spin-echoes. The thickness of the selected plane was 8 mm and its orientation was in a tilted coronal plane along the anterior border of the brainstem, perpendicular to and at the level of the body of the hippocampus. The T2 relaxation time in milliseconds was displayed as pixel intensity on a map and the hippocampal T2 relaxation time was read using the largest possible region of interest placed within the hippocampus, avoiding boundaries where partial volume effects with cerebrospinal fluid may occur (Fig. 1B).

Statistical analysis
Multiple linear regression and general linear modelling using SPSS for Windows (version 10) were carried out to identify differences in T2 relaxation time or hippocampal volume between patient and control groups after adjustment for age and/or intracranial volume. The mean of right and left measurements in each individual was used. Variables investigated included age, intracranial volume, time from acute insult to scan and seizure length, as well as interaction terms. A simple comparison of covariate adjusted means was not possible, however, because the patient groups exhibit a T2 dependence on time from acute event to scan, and time from event to scan is not meaningful in the control subjects.
Nevertheless, a simple and robust comparison of control subjects and patients can be achieved by treating the time to scan as a categorical variable. Accordingly, the variable, time from event to scan, was converted to a binary variable using a 2-day cut-off point (time to scan of 2 days, i.e. \(< 48\) h, or time to scan more than 2 days, i.e. \(> 48\) h) thus generating three groups: control, early-investigated and late-investigated patients. The resulting one-way comparison between groups was performed using the standard general linear models approach. A transformation of the form \(-\log (137-T_2)\) was used on the \(T_2\) relaxometry data and revealed the best distribution of residuals. A Bonferroni correction for multiple comparisons was performed.

The control subjects at 102 and 105 months of age were excluded from the analysis of the PFC group, but not the analysis of the ASE group, as they were outside the age range of interest (the oldest patient in group PFC was 31 months).

Asymmetry of \(T_2\) relaxation time and HCV was investigated by analysing the ratio of larger to smaller values with a Mann–Whitney \(U\) test (defined as \(T_2\) ratio and HCV ratio, respectively). Values that lay outside the 95th percentile for control subjects were considered abnormal.

**Results**

Thirty-five patients were enrolled into the study. Of these, 21 had a history of a generalized PFC (group PFC, 12 males) and 14 had generalized ASE (group ASE, five males). Of those in the latter group, four had idiopathic SE, two had acute symptomatic SE and eight had remote symptomatic SE. Those children with acute symptomatic and idiopathic status epilepticus were developmentally normal, while those with remote symptomatic status epilepticus all had global developmental delay. The over-representation of patients with remote symptomatic status epilepticus in this study is probably due to a referral bias of children with more severe disorders at Great Ormond Street Hospital. In group PFC, all except two patients were investigated following their first PFC. None had afebrile seizures prior to the event. In group ASE, all children were investigated following the first episode of status epilepticus and five had a previous history of short afebrile seizures. All seizures were generalized at the time they were first observed, but the onset of the seizure was not usually witnessed. No focal neurological deficits at the termination of status epilepticus were noted in any child.

The median age [and interquartile range (IQR)] of the patients in group PFC was 16 (12–23) months, and they had an intracranial volume (ICV) of 1201 (1095–1311) cm\(^3\). They had a seizure length of 45 (30–90) min and underwent MRI investigations within 2 (range 1–5) days from the time that the seizure terminated.

The median (IQR) age of the patients in group ASE was 26.5 (14.7–60) months and they had an ICV of 1151 (1000–1409) cm\(^3\). They had a seizure length of 52.5 (33.7–97.5) min and underwent MRI investigations within 2 (range 1–5) days from the time of seizure termination.
There were 10 control subjects who had T2 relaxometry with a median (IQR) age of 17.5 (7–66) months, and nine who had hippocampal volumetry with an age of 20 (7–54) months and an ICV of 1132 (855–1313) cm³.

Visual assessment of MRI

MRI investigations were performed in all 35 patients. On visual inspection, 13 out of 35 scans were reported as having an abnormality. Five of the 21 patients from group PFC had an abnormality. Of these, three were reported as having hippocampal asymmetry (subsequently two were found to have asymmetry on quantitative assessment), one had a left temporoparietal arachnoid cyst and one had subtle loss of grey-white matter differentiation in the left middle temporal gyrus.

A wide range of abnormalities were identified in eight out of 14 of the patients in group ASE. One patient was reported to show hippocampal asymmetry but no other patients had hippocampal or temporal lobe abnormalities. One patient with remote symptomatic status epilepticus had evidence of delayed myelination. She was developmentally delayed in all domains. There was one patient with bilateral signal increases in T2-weighted imaging in both thalami who had profound developmental delay. Two patients had occipital lobe abnormalities; one had a posterior circulation infarct and one had an area of cortical dysplasia. One patient with developmental delay had evidence of an old left hemisphere cerebellar infarct. The final patient, with juvenile chronic arthritis, had bilateral parietal T2 signal abnormalities, consistent with a cerebral vasculitis.

Quantitative assessment

In group PFC, age and intracranial volume were significant predictors of HCV, but time from insult to scan (P = 0.28) and seizure length (P = 0.14) were not. Age was a significant predictor of T2 relaxation time. In addition, there was a decrease in T2 relaxation time with increasing time from acute insult to investigation (P = 0.024). Seizure length was not a significant predictor of T2 relaxation time (P = 0.28).

After correction for age and ICV, HCV was a mean of 232 mm³ [95% confidence interval (CI) = 93–371 mm³] larger than HCV in control subjects (P = 0.004; Fig. 2). Time from insult to scan needed to be taken into account in the analysis of T2 relaxation time in patients from group PFC. The three groups consisting of control subjects, early investigated PFC and late investigated PFC are distinguishable (general linear model, P = 0.01; Fig. 3). There is evidence for prolongation of T2 relaxation time in the early-investigated patients from group PFC when compared with control subjects (P = 0.048; Fig. 3). As T2 relaxation time would be expected to increase in both oedema and gliosis, one-sided P-values after correction for multiple comparisons are reported. There was no difference between late-investigated patients and control subjects (P = 0.90; Fig. 3). As the T2 relaxation time data were transformed to normalize residual distributions, means and confidence intervals are not reported. T2 and HCV ratios were similar in group PFC and control subjects (P = 0.36 for
T2 and P = 1.0 for HCV). Three patients had abnormal HCV ratio and two of these were identified on visual assessment. No patient had a T2 ratio abnormality.

In group ASE, age and ICV were significant predictors of HCV, but time to scan (P = 0.12) and seizure length (P = 0.12) were not. Age was a significant predictor of T2 relaxation time, but time to scan (P = 0.24) and seizure length (P = 0.12) were not. After correction for age and ICV, HCV in group ASE was not different from that in control subjects (P = 1.0; Fig. 4). After correction for age, T2 relaxation time was prolonged by a mean of 8.8 ms (95% CI = 2.4 – 15.0 ms) when compared with control subjects (P = 0.02; Fig. 5). T2 and HCV ratios were similar in group ASE and control subjects (P = 0.50 for T2 and P = 0.62 for HCV). Only one patient had an abnormal HCV ratio and one patient had an abnormal T2 relaxation time ratio. These were not the same patients and neither were identified on visual assessment.

Discussion

MTS is the most common structural abnormality identified in patients who undergo temporal lobe resections for medically intractable epilepsy (Cendes et al., 1993). There are human and animal data that support the view that MTS is associated with convulsive status epilepticus, especially febrile convulsion in childhood (Cavanagh and Meyer 1956; Davies et al., 1996). There is continued debate on whether there is a causative association between status epilepticus and MTS.

The aim of this study was to perform qualitative and quantitative analysis using MRI techniques within 5 days of an acute event to investigate whether status epilepticus is associated with hippocampal abnormalities.

The major findings in the patients from group PFC suggest that PFC is acutely associated with hippocampal oedema. There are three strands of evidence that support this view. There is strong evidence for large HCV in group PFC compared with control subjects. In addition to large HCV, the T2 relaxometry data in this patient group suggest a prolongation of T2 relaxation time in those patients who were scanned within 2 days, but such an increase in T2 relaxation time was not detected in those who were investigated after a period of >2 days; there is a significant decrease in T2 relaxation time with increasing time from the acute insult to MRI investigations. This combination of findings is suggestive of hippocampal oedema, which resolves within a 5 day period, albeit with T2 relaxation time and HCV resolving at different rates. In a recent report (VanLandingham et al., 1998), four out of 15 patients with a history of prolonged lateralized febrile seizures, but none out of 15 patients with prolonged generalized febrile seizures, had evidence of hippocampal asymmetry consistent with swelling. In that study, however, hippocampal volumes were not analysed as absolute volumes but as hippocampal volume ratios, and T2-weighted MRI scans were analysed visually for increase in hippocampal T2 signal. The methodology, therefore, was not ideally suited to the identification of bilateral abnormalities, as bilaterally
large hippocampi would not be identified using hippocampal volume ratios. The sensitivity of qualitatively assessed T2-weighted MRI would also be reduced if both hippocampi were hyperintense.

An alternative explanation of these findings is that patients who had a PFC have pre-existing hippocampal dysgenesis. However, it is unlikely that a chronic abnormality in T2 relaxation time would return to normal within 5 days of an acute event unless T2 relaxation time was influenced by that acute event. In addition, given the findings in this study, the pre-existing hippocampal dysgenesis hypothesis would imply that many patients undergoing MRI within an epilepsy surgery programme would have evidence of large or large and bright hippocampi, particularly on the side contralateral to the seizure focus. As far as we are aware there are no data from the literature supporting the view that such hippocampal abnormalities are found in patients with chronic epilepsy. It is possible that such hippocampi have not been identified in patients with chronic epilepsy as recurrent seizures may cause ongoing hippocampal damage. However, a recent study, in which patients were investigated a mean of 11 days from the acute event, revealed hippocampal asymmetry but no evidence of large hippocampi (Grünewald et al., 2001). Therefore, although a pre-existing hippocampal abnormality cannot be ruled out, hippocampal oedema appears to be the most likely cause of the abnormalities identified in the current study.

It has been suggested that MTS may be present at the time of PFC, which implies that it is possible to use MRI to identify MTS at the time of an acute insult. Although three patients in group PFC were reported qualitatively to have hippocampal asymmetry, it is important to note that no patient in the current study was shown to have evidence of MTS on acute imaging, i.e. pathologically small hippocampus with associated hyperintensity in T2-weighted images (Jackson et al., 1993). Quantitative assessment did not reveal any hippocampus that was small when compared with control subjects.

There were only two other patients in group PFC with reported abnormalities on visual assessment. One showed subtle loss of grey-white matter differentiation in the middle temporal gyrus, which may be a weak marker of temporal lobe oedema. The other had an arachnoid cyst, which is unlikely to have a causative association with a PFC.

In contrast to the patients with PFC, those with ASE had a wide variety of abnormalities identified on visual inspection of the MRI. There was only one patient with reported hippocampal abnormalities, i.e. hippocampal asymmetry, but again this asymmetry was not consistent with MTS. There were seven patients with abnormalities outside of the hippocampus or temporal lobe: one may have had acute abnormalities that resulted from the prolonged seizure (thalamic hyperintensity), two had acute intracranial processes that may have caused the prolonged seizure (posterior circulation infarct and cerebral vasculitis), and three almost certainly had pre-existing abnormalities. The patient with T2 signal hyperintensity in the thalamus bilaterally had findings consistent with acute thalamic injury identified in animal models of limbic status epilepticus (Meldrum, 1997).
Quantitative hippocampal assessment in the patients with ASE indicated that as a group they had significantly prolonged T2 relaxation times, but that their hippocampal volumes were normal when compared with those of control subjects. Given the prolonged T2 relaxation time and that the majority of the group had remote symptomatic status epilepticus and global developmental delay (eight out of 14), it is possible that prolongation of the T2 relaxation time, rather than being an acute response to status epilepticus, primarily reflects a pre-existing brain abnormality or immaturity, associated clinically with a learning disability. This hypothesis will need to be tested in future studies.

This study suggests that PFC in childhood is associated with acute hippocampal oedema, suggested by hippocampal enlargement in association with prolongation of T2 relaxation time, which declines within days of PFC; ASE, however, is not. This is consistent with previous epilepsy surgery series, which suggest that the association between PFC and MTS is stronger than the association between ASE and MTS. Follow-up scans will be required to determine how the hippocampi in these patient groups evolve and in particular whether any patient develops MTS.

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