Hippocampal Apparent Diffusion Coefficient Following Prolonged Febrile Convulsion in Childhood

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RATIONALE: Prolonged febrile convulsion (PFC) is the most common type of convulsive status epilepticus in children and usually has an excellent prognosis. However, there is a history of PFC in approximately 50% of patients with hippocampal sclerosis, the most common structural substrate identified in patients that undergo epilepsy surgery, and there is a longstanding hypothesis that this relationship may be causative. There is now mounting evidence that PFC causes acute hippocampal oedema (prolonged T2 relaxation time and large hippocampal volume) that may be the first part of the pathophysiological sequence that links PFC to hippocampal sclerosis, although the nature of that oedema remains uncertain. In studies of cerebral ischaemia, a reduction in the apparent diffusion coefficient (ADC) is believed to be indicative of cytotoxic oedema, whereas the later increase in ADC is attributed to vasogenic oedema following cell membrane disruption. In epilepsy, acute reduction of ADC in the cerebral cortex has been observed in animal models of convulsive status epilepticus, and has been attributed to cell swelling following movement of water from extra- to intra-cellular space as a result of disruption of ion homeostasis. A common process recognised in both ischaemia and epilepsy is the presence of cell swelling, suggesting a similar underlying association between ADC reduction and cytotoxic oedema in both cases. Thus, the hippocampal diffusion characteristics associated with PFC may be useful in the understanding of the mechanisms of oedema. The principal aims of the current study were: (1) to use ADC measurements to further characterise the hippocampal oedema previously identified within 5 days of a PFC, and (2) to determine whether any ADC abnormalities identified have evolved within 4-8 months. It has been shown that the ADC decreases with increasing age in many brain regions, but to date this has not been characterised in the hippocampus. Therefore, in order to achieve our primary goal, an additional aim was to characterise the age dependency of hippocampal ADC during the first 3 years of life.

METHODS: 23 patients were investigated (median age 18 months, range 7-21 months) within 5 days of a PFC, and in 14 of these children a mean of 5.5 months later. 20 control subjects (median age 12 months, range 6-39 months), identified from children undergoing scans for other reasons e.g. skin lesions suggestive of neurocutaneous disorders and those with eye or ear abnormalities were also enrolled. These children were all otherwise neurologically normal and had normal MR brain imaging on visual assessment. Axial diffusion imaging was performed using a FLAIR spin-echo diffusion weighted EPI sequence, with a pair of diffusion gradients on either side of the refocusing pulse. The imaging parameters were; TE/TR = 86/8700 msec, inversion time (TI) = 2100 msec, 128 x 128 matrix, 24 cm FOV, 5 mm slice thickness, 1 mm gap between slices. The diffusion parameters were; diffusion gradient duration (δ) = 15 msec, time interval between diffusion gradients (Δ) = 50.2 msec, b values = 0 and 617 sec/mm^2. Maps of the apparent diffusion coefficient were calculated online in three orthogonal directions, which were combined to generate average ADC maps to eliminate the confounding effects of diffusion anisotropy. A region of interest was then drawn on the ADC map, within the hippocampus, and the ADC from that region of interest was read from the ADC map.

RESULTS: The PFC was generalised at the time it was first observed in all patients. 3 children had a further PFC between the magnetic resonance investigations. One patient has developed non-febrile seizures, with no associated structural brain abnormality. On a paired analysis there is a reduction in ADC between the acute and follow-up investigations in patients investigated within 2 days of a PFC ($p=0.048$), but not in those children investigated 3-5 days after the PFC ($p=0.9$), see Figure 1. In control subjects there is a strong dependence of ADC on age ($p = 0.001$) but no age dependence was identified in patients at the initial timepoint ($p=0.26$) or at follow-up ($p=0.66$). There was an interaction between the group into which an individual fell (i.e. patient or control subject) and age at which the MRI was carried out ($p = 0.029$), i.e. the behaviour of ADC with respect to age was different in patients when compared to control subjects, see Figure 2.

CONCLUSION: The 2 major findings in the current study are (1) the reduction in ADC over time in patients investigated within 2 days of a PFC but not in those investigated 3-5 days after the event, and (2) the difference in the age trajectory between patients and controls. The reduction in ADC over time provides additional evidence for hippocampal oedema within 2 days of PFC, and suggests that it is vasogenic in nature. The oedema has largely resolved within 5 days of the PFC. The difference in the dependence of ADC upon age in the children with a PFC, compared to control subjects, at either the initial or follow-up timepoints, suggests that hippocampal development may be abnormal in children who are prone to PFC. Understanding the cellular mechanisms for such developmental differences may provide insight into mechanisms of a predisposition to PFC, with important implications for the most common form of drug resistant epilepsy.

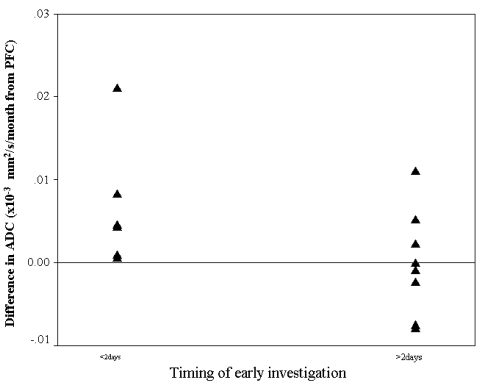

Figure 1. Scatterplot of difference in ADC between first and second investigations, after adjustment for time between investigations, in patients who were initially investigated within 2 days of a prolonged febrile convulsion and in those children whose initial investigation was between 3 and 5 days after the prolonged febrile convulsion. A reduction in ADC between the two investigations results in data that lie above the reference line.

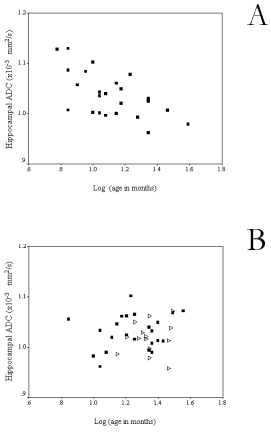

Figure 2. Scatterplots of hippocampal ADC against age in control subjects (A), in patients imaged within 5 days of a prolonged febrile convulsion (B, solid squares; data adjusted for time in days between PFC and initial imaging investigations) and patients imaged 4-8 months after a prolonged febrile convulsion (B, open triangles).