Childhood seizures and their consequences for the hippocampus

Both idiopathic generalized epilepsy and focal epilepsy may be associated with seizures in early childhood (Hamiati-Haddad and Abou-Khalil, 1998). The majority of adults with refractory epilepsy have focal epilepsy, with a temporal lobe epileptic focus in ~60–70% of which hippocampal (mesial temporal) sclerosis is the causative lesion in ~80% (Van Paesschen et al., 1995). In newly diagnosed focal epilepsy the prevalence of hippocampal sclerosis is ~11% (Van Paesschen et al., 1998). The aetiology of this common cause of focal epilepsy remains enigmatic. One of the few clues is its association with early childhood convulsion (ECC), particularly complicated ECC (usually defined as lasting >15 min, associated with focal neurological deficit or recurrent within 24 h). Approximately half of patients with hippocampal sclerosis report a history of complicated ECC (Kuks et al., 1993), and 90% of patients with temporal lobe epilepsy and a history of complicated ECC have hippocampal sclerosis (Grünewald et al., 1994).

ECCs affect between 2 and 4% of the population and are usually benign. However, after an ECC a small minority of children continue to have seizures or develop epilepsy later. The Child Health and Education Study, a birth cohort study, demonstrated that the risk of epilepsy depends on the type of seizure, being higher for complicated than simple ECCs, (4–6% versus 1–1.5% risk of epilepsy in the first 10 years of life; Verity and Golding, 1991). Such complicated convulsions are uncommon, making up only ~6% of ECCs. Other studies have demonstrated that the prognosis of seizures with multiple complicating features (Annegers et al., 1987) and childhood febrile status epilepticus (Maytal and Shinnar, 1990) is also worse than that of briefer seizures. Published prospective studies are too short to estimate and analyse the full risk of developing epilepsy, let alone hippocampal sclerosis, after ECC, as hippocampal sclerosis may not present until the third decade of life.

Although the association of hippocampal sclerosis with temporal lobe epilepsy has been recognised for over 100 years, it has received little prominence in medical textbooks until the last decade, because only since the early 1990s has it been possible to diagnose the condition in life by MRI, using the diagnostic features of loss of hippocampal volume, loss of visible internal hippocampal structure, high T2 signal and low T1 signal (Jackson et al., 1990). Several MRI-based studies have now been published which address the relationship between ECC and hippocampal damage. As frank hippocampal sclerosis is rarely observed in children under 2 years of age, MRI studies of childhood seizures have concentrated on subtle pathology, such as hippocampal volume asymmetry or T2 signal abnormality, which may progress to hippocampal sclerosis.

Frequent seizures or status epilepticus in infancy do not necessarily lead to hippocampal sclerosis (Kothare et al., 2001). This begs the questions of whether, or in what circumstances, seizures damage the hippocampus, or whether complicated ECCs are just indicative of pre-existing brain abnormality. Our study of children within 2 weeks of their first complicated ECC suggested that hippocampi in a high proportion of such children are already abnormal, i.e. asymmetric (Grünewald et al., 2001). This asymmetry could not be attributed to oedema, as hippocampal T2 relaxation times were symmetrical. These children also had a high prevalence of other brain abnormalities on MRI, and we concluded that complicated ECC was often a marker for pre-existing brain pathology. The data also suggested that febrile complicated ECCs were more strongly associated with hippocampal asymmetry than afebrile seizures. A study of adults demonstrated hippocampal asymmetry only in those with a history of ECC associated with fever, and the authors suggested that it was possible that fever influenced hippocampal damage (Kuks et al., 1993). Such a suggestion is consistent with experimental evidence from animals (Meldrum and Brierley, 1973), but is not the only interpretation of the data.

In this issue of Brain, Scott and co-workers, using multiple linear regression, report enlarged hippocampi with higher T2 relaxation time in children after a prolonged generalized convulsion (Scott et al., 2002). In children who were febrile at the time of the prolonged seizure, the hippocampal T2 relaxation time reduced with time from seizure, implying gradual resolution of oedema. A relevant study of complicated ECC has been published previously (Van Landingham et al., 1998). In this study, two patients with lateralized seizures had bilaterally small hippocampi. The remaining four had increased hippocampal volumes ipsilateral to the seizure focus. This was attributed to oedema, as visual inspection of the MRI also suggested increased hippocampal T2 signal. Two of the four patients with large hippocampi on

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the side of the seizure focus underwent repeat MRI after 8–10 months and both then showed hippocampal atrophy ipsilateral to the seizure focus. One of these patients was rescanned 25 months after the initial MRI. The affected hippocampus had grown, but failed to reach the normal volume range.

Whilst prolonged convulsions associated with fever may be particularly harmful to the hippocampus and produce damage characterized in the early stages by hippocampal oedema, the situation is not straightforward. Scott et al. (2002) found no evidence that hippocampal ‘swelling’ resolved over the 5-day time-course of the study in parallel with the reduction in hippocampal T2 relaxation time in their subjects. Neither was there a time-dependent reduction in the abnormal hippocampal T2 relaxation time found in febrile patients after status epilepticus. This leaves open the possibility that the hippocampi were intrinsically abnormal independent of oedema in some patients, i.e. slightly large or bright on T2-weighted images.

Any theory of the aetiology of hippocampal sclerosis must also account for its characteristic asymmetry. There is evidence that hippocampal abnormalities may be familial (Kobayashi et al., 2001). Significant hippocampal asymmetry has also been demonstrated in asymptomatic relatives of probands with hippocampal sclerosis (Fernandez et al., 1998). It is plausible that such abnormal hippocampi might be epileptogenic if a child is febrile.

Do recurrent seizures damage the hippocampus further? Some evidence suggests they may: the severity of hippocampal volume loss correlates with the number of secondary generalized seizures in the patient’s lifetime (Van Paesschen et al., 1997), and the duration of epilepsy correlates with hippocampal volume ipsilateral to the seizure focus (Theodore et al., 1999).

It seems likely that complicated ECC or childhood status epilepticus can produce transient hippocampal oedema. This and subsequent seizures may damage the hippocampus ultimately producing hippocampal sclerosis. However, ECCs are neither necessary nor sufficient to explain hippocampal sclerosis which often exists in patients with no history of ECC. ECCs often occur in the context of an already abnormal brain. We may have to look earlier in development towards an embryological aetiology of hippocampal dysgenesis to identify the true origins of hippocampal sclerosis (Vernet et al., 2000).

Richard Grünwald
Department of Neurology
Royal Hallamshire Hospital
Sheffield, UK

References


