IS MESIAL TEMPORAL SCLEROSIS A NECESSARY COMPONENT OF TEMPORAL LOBE EPILEPSY?

Temporal Lobe Epilepsy after Experimental Prolonged Febrile Seizures: Prospective Analysis

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Experimental prolonged febrile seizures (FS) lead to structural and molecular changes that promote hippocampal hyperexcitability and reduce seizure threshold to further convulsants. However, whether these seizures provoke later-onset epilepsy, as has been suspected in humans, has remained unclear. Previously, intermittent EEGs with behavioural observations for motor seizures failed to demonstrate spontaneous seizures in adult rats subjected to experimental prolonged FS during infancy. Because limbic seizures may be behaviourally subtle, here we determined the presence of spontaneous limbic seizures using chronic video monitoring with concurrent hippocampal and cortical EEGs, in adult rats (starting around 3 months of age) that had sustained experimental FS on postnatal day 10. These subjects were compared with groups that had undergone hyperthermia but in whom seizures had been prevented (hyperthermic controls), as well as with normothermic controls. Only events that fulfilled both EEG and behavioural criteria, i.e. electro-clinical events, were considered spontaneous seizures. EEGs (over 400 recorded hours) were normal in all normothermic and hyperthermic control rats, and none of these animals developed spontaneous seizures. In contrast, prolonged early-life FS evoked spontaneous electro-clinical seizures in 6 out of 17 experimental rats (35.2%). These seizures consisted of sudden freezing (altered consciousness) and typical limbic automatisms that were coupled with polyspike/sharp-wave trains with increasing amplitude and slowing frequency on EEG. In addition, interictal epileptiform discharges were recorded in 15 (88.2%) of the experimental FS group and in none of the controls. The large majority of hippocampally-recorded seizures were heralded by diminished amplitude of cortical EEG, that commenced half a minute prior to the hippocampal ictus and persisted after seizure termination. This suggests a substantial perturbation of normal cortical neuronal activity by these limbic spontaneous seizures. In summary, prolonged experimental FS lead to later-onset limbic (temporal lobe) epilepsy in a significant proportion of rats, and to interictal epileptifom EEG abnormalities in most others, and thus represent a model that may be useful to study the relationship between FS and human temporal lobe epilepsy.

COMMENTARY

Temporal lobe epilepsy (TLE) is a syndrome characterized by recurrent complex auras, complex partial seizures, and secondarily generalized seizures; characteristic memory deficits; abnormalities in EEGs (recorded interictally and during seizures); and specific brain lesions, detected during MRI and neuropathological examination. Many patients with TLE do not respond to antiepileptic drugs and are referred to tertiary medical centers, where they undergo a series of tests to localize and define the site of seizure onset. Those who meet certain criteria are offered temporal lobectomy for control of seizures. The current understanding of TLE is strongly influenced by the intense study of patients evaluated for surgery in academic medical centers. However, these patients likely represent a subset of the population of patients with TLE.

The neuropathological lesion associated with TLE, mesial temporal sclerosis, is characterized by gliosis as well as the loss of CA1 and CA3 pyramidal neurons and hilar neurons. In addition, sprouting of mossy fibers (the axons of granule cells) is often found in specimens removed from patients with TLE. The association of this neuropathology with TLE was based on autopsy studies performed in late nineteenth and early twentieth

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century and on more recent studies of specimens removed during surgery for medically intractable TLE. However, these association studies per se, do not establish that neuronal loss and axonal sprouting are necessary accompaniments to TLE. In fact, many patients undergoing surgery have clinical features of TLE, but their resected hippocampi show no evidence of neuronal loss or axonal sprouting, which has led to use of the term "paradoxical TLE" for these patients, based on the paucity of expected neuronal loss (1). However, clinical experience suggests that absence of mesial temporal sclerosis in patients with TLE may be more common than previously suspected. MRI scans can sensitively detect mesial temporal sclerosis, and many patients with clinical features of TLE have no evidence of sclerosis on their scans.

The prevailing wisdom that mesial temporal sclerosis is the key neuropathological lesion underlying TLE has strongly influenced first generation animal models of this disease. Several animal models of TLE have developed over last 20 years, including electrical stimulation models; in addition, kainate and cholinergic stimulation models (pilocarpine and lithium/pilocarpine) are characterized by recurrent spontaneous limbic seizures, varying degrees of loss of CA1 and CA3 pyramidal neurons as well as of hilar neurons, and sprouting of mossy fiber axons.

In several animal models, recurrent spontaneous limbic seizures developed without characteristic neuropathological findings of mesial temporal sclerosis. In one model, 20-day-old rat pups were subjected to prolonged seizures, induced by lithium and pilocarpine, and examined as adults (2). Two-thirds of the animals subjected to early life status epilepticus developed recurrent spontaneous limbic seizures, which in some cases progressed to stage V seizures. The authors found no evidence of mesial temporal sclerosis and mossy fiber sprouting in two-thirds of the animals with recurrent spontaneous seizures. In the remaining animals, CA1 and CA3 cell loss and/or mossy fiber sprouting were found.

In the current study by Dube et al., 10-day-old pups were subjected to prolonged febrile seizures and allowed to grow to adulthood, at which point video EEG recordings were taken, using a pair of hippocampal and cortical electrodes, and behavior was monitored for 5 hours each night. Recurrent spontaneous hippocampal seizures associated with behavioral manifestation of freezing and automatisms were recorded from one third of all animals studied. No secondarily generalized tonic–clonic (grade IV or V, Racine scale) seizures were recorded from these animals (3). There was no evidence of neuronal loss or sprouting in any epileptic animal. In addition to these studies, previous studies have raised questions about the relationship of cell loss and mossy fiber sprouting to the pathogenesis of recurrent spontaneous seizures. In kainate and electrical stimulation models of epilepsy, the extent of cell loss varies significantly from animal to animal, including examples of TLE without cell loss. Similarly, dissociation between epileptogenesis and mossy fiber sprouting has been described in these models.

The role of neuronal loss and mossy fiber sprouting in expression of epilepsy has been studied in a novel kainate model (4). In this important study, rats were made epileptic by a single injection of kainate (10 mg/kg), leading to prolonged status epilepticus (1 KA group). A second group of rats were given kainate (10 mg/kg) three times; seizures were aborted following the first two kainate injections but were allowed to continue for several hours following the third injection (3 KA group). The 1 KA animals developed characteristic features of mesial temporal sclerosis. By contrast, 3 KA animals did not show any of these changes in their hippocampi. Although both the 3 KA and 1 KA groups developed recurrent spontaneous seizures, there were differences in the way epilepsy progressed. Both groups showed similar frequency of Racine scale grade 2–3 seizures. The mean frequency of grade 4–6 seizures was also similar for first 8 weeks after KA administration. However, the frequency of grade 4 seizures increased dramatically (4-fold) in the 1 KA group, whereas the frequency of seizure in the 3 KA group that lacked neuropathology remained unchanged. Similarly, the duration of electrographic seizures was significantly longer in the 1 KA group than in the 3 KA group, further suggesting a more severe form of epilepsy.

The emerging evidence, therefore, suggests that cell loss and mossy fiber sprouting are not absolutely necessary for the generation of recurrent spontaneous limbic seizures. However, these neuropathological findings perhaps indicate a more refractory or progressive form of TLE. The neuropathology is commonly seen in surgical specimens because patients refractory to medical therapies are selected for surgery. Such a hypothesis may be tested by prospective clinical studies that evaluate MRI of patients with well-controlled and medically refractory TLE. Similarly, it would be interesting to test whether seizures occurring in animal models of TLE without mesial temporal sclerosis are easily controlled by antiepileptic drugs.

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