APOE, MEMORE, AND EPILEPSE

ApoE-ϵ4 Is Associated with Reduced Memory in Long-Standing Intractable Temporal Lobe Epilepsy. Busch RM, Lineweaver TT, Naugle RI, Kim KH, Gong Y, Tilelli CQ, Prayson RA, Bingaman W, Najm IM, Diaz-Arrastia R. *Neurology* 2007;68(6):409–414. OBJECTIVE: To investigate the relationship between the apolipoprotein (ApoE) 4 allele and memory performance (verbal and nonverbal) in patients with medically intractable temporal lobe epilepsy (TLE) who underwent temporal lobectomy. METHODS: Presurgical and postsurgical memory performance was examined in 87 adult patients with TLE (4 = 22; non-4 = 65) to determine whether the expression of ApoE-4 may be associated with memory performance in this population and to examine how this relationship may be affected by duration of epilepsy. RESULTS: There was a significant interaction between ApoE-4 status and duration of epilepsy such that 4 carriers with a long duration of epilepsy demonstrated the poorest memory performance on both verbal and nonverbal measures. This relationship was observed both before and after temporal lobectomy, with little change in test performance over time. CONCLUSIONS: The ApoE-4 allele interacts with longstanding seizures to affect memory performance, both verbal and nonverbal, in patients with medically intractable temporal lobe epilepsy.

COMMENTARY

Apolipoprotein E (better known as ApoE) is of interest to virtually all neurologists and neuroscientists, as it plays a crucial role in lipid transport and homeostasis, maintenance of synaptodendritic connections, and repair of neurons after all types of injuries or stress (1). ApoE is synthesized in the liver and brain. In the brain, its main producer is the astrocyte, although neurons can also synthesize ApoE after injury. ApoE mRNA is found in the cortex and hippocampus in humans. ApoE synthesis is induced in rat hippocampal neurons after kainic acid and in human cortical neurons after infarction. The gene for ApoE (*APOE*) on chromosome 19 encodes three alleles: ApoE ϵ2, ApoE ϵ3, and ApoE ϵ4. The ApoE ϵ4 allele is the least effective of the isoforms, and when present, the result is decreased enzymatic activity of ApoE and, therefore, decreased ability to protect and repair neurons. In addition, there is some evidence that the ApoE ϵ4 isoform is particularly susceptible to proteolysis to neurotoxic fragments (1).

The ApoE ϵ4 allele first received neurological notoriety when it was recognized that its presence was a major risk factor for Alzheimer's disease. Fortunately, the more effective ApoE ϵ3 allele (associated with greater ApoE enzymatic activity and better neuronal protection and repair than ϵ4) is the most common allele, with at least half the population having the ϵ3/ϵ3 genotype (2). However, at least one ApoE ϵ4 allele is present in 15 to 20% of people (1). These individuals have double the risk of Alzheimer's disease: 45% by age 85, compared with 20% for the overall population. The 2% of the population with ϵ4/ϵ4 have a 50 to 90% chance of developing Alzheimer's by age 85 (3). Among patients with Alzheimer's disease, 40 to 80% have an ApoE ϵ4 allele, and it is associated with earlier age of onset (1).

But ApoE ϵ4's harm is not limited to Alzheimer's disease. It has been shown to be associated with the following negative neurological effects, among others: greater memory decline in healthy subjects; increased risk of infarct, obstructive sleep apnea, Parkinson's disease, Lewy Body disease and frontal lobe dementia; worse neurological outcome after traumatic brain injury (including boxing), intracerebral hemorrhage, and subarachnoid hemorrhage (2); more rapid progression of disability in multiple sclerosis; and increased cognitive deficits associated with sleep apnea (4) and cardiac surgery.

What about epilepsy? It was previously shown that the ApoE ϵ4 allele is associated with increased β-amyloid deposition in the form of senile plaques in patients with intractable epilepsy: 70% of patients with plaques had at least one ApoE ϵ4 allele compared with 27% of those without plaques (5). One study found a shorter "silent interval" between early life insult and intractable seizures in those with ApoE ϵ4 compared with those without (6), and another study similarly found an earlier age of onset of intractable seizures (7). Patients with temporal lobe epilepsy and ApoE ϵ4 are at greater risk of verbal learning deficits (50% of patients with ApoE ϵ4 had these deficits compared with 19% of those without), especially those with longer duration of epilepsy (7). One investigation of patients with

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cryptogenic complex partial seizures reported a greater chance of being refractory to treatment in patients with an ApoE $\epsilon 4$ allele: 40% of refractory patients were ApoE $\epsilon 4$ positive compared with 7% of those who were well controlled (8). The ApoE isoform is probably not a risk factor for epilepsy itself, except for posttraumatic epilepsy in which the presence of ApoE $\epsilon 4$ is associated with more than doubling of the risk of late seizures, as reviewed in *Epilepsy Currents* in 2004 (9,10).

In the current study, Busch et al. expand upon the correlation between ApoE $\epsilon 4$ and memory dysfunction in chronic temporal lobe epilepsy by studying adults undergoing temporal lobectomy before and after surgery. In those without ApoE $\epsilon 4$, there was no correlation at all between duration of epilepsy and memory scores. However, among patients with ApoE $\epsilon 4$, there was a clear and significant correlation. Patients with a long (>22 years) duration had lower scores on all five memory indices (verbal and nonverbal) compared to those with shorter duration. Surgery had minimal effect on memory. The authors calculated that the ApoE $\epsilon 4$/duration-of-epilepsy interaction accounted for 18% of the variance in memory scores. They theorize that medically refractory seizures are a form of repetitive brain injury, similar to repetitive head trauma, and thus it is not surprising that repair mechanisms (for which ApoE function is vital) would be important determinants of pathology and dysfunction.

All of the above studies support the notion that ApoE status is an important determinant of the brain's response to injuries, including repetitive seizures. When ApoE function is inadequate as a result of the presence of an ApoE $\epsilon 4$ allele, the brain is less able to deal with a variety of stresses. Thus, after brain injury, seizures are more likely to develop in the presence of ApoE $\epsilon 4$ and to become refractory; amyloid deposition is more apt to occur; and there is a greater chance that temporal lobe dysfunction will develop over time. These findings raise the possibility of early identification of at-risk groups and therefore of early intervention—potentially preventing some cases of epilepsy, improving response to treatment, and ameliorating associated cognitive dysfunction. Fortunately, research into the mechanisms of ApoE is progressing rapidly. It may be possible to convert the ApoE $\epsilon 4$ isoform into an ApoE $\epsilon 3$-like form to block proteolysis of ApoE or to upregulate ApoE function in other ways (1). Advances in this area are likely to be widely applicable throughout neurology, including epilepsy.

by Lawrence J. Hirsch, MD

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Transcranial Magnetic Stimulation and Sleep Deprivation as Experimental Tools: When Sleep Deprivation Is Too Exciting

Sleep Deprivation Increases Cortical Excitability in Epilepsy: Syndrome-Specific Effects. Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. *Neurology* 2006;67(6):1018–1022. OBJECTIVE: To use transcranial magnetic stimulation (TMS) to investigate the hypothesis that sleep deprivation increases cortical excitability in people with epilepsy. METHODS: We performed paired pulse TMS stimulation, using a number of interstimulus intervals (ISIs) on each hemisphere of 30 patients with untreated newly diagnosed epilepsy (15 idiopathic generalized epilepsy [IGE] and 15 focal epilepsy) and on the dominant hemisphere of 13 healthy control subjects, before and after sleep deprivation. RESULTS: Both hemispheres in patients with IGE and the hemisphere ipsilateral to the EEG seizure focus in those with focal epilepsy showed an increase in cortical excitability following sleep deprivation at a number of ISIs. This change in excitability was most prominent in the patients with IGE. Although there were minor changes after sleep deprivation in control subjects and the contralateral hemisphere in the focal epilepsy group seen at the 250-millisecond ISI, it was less than that in the other groups. CONCLUSIONS: Sleep deprivation increases cortical excitability in epilepsy; the pattern of change is syndrome dependent.

Effects of Sleep Deprivation on Cortical Excitability in Patients Affected by Juvenile Myoclonic Epilepsy: A Combined Transcranial Magnetic Stimulation and EEG Study. Manganotti P, Bongiovanni LG, Fuggetta G, Zanette G, Fiaschi A. *J Neurol Neurosurg Psychiatry* 2006;77(1):56–60. OBJECTIVE: To investigate the effect of sleep deprivation on corticospinal excitability in patients affected by juvenile myoclonic epilepsy (JME) using different transcranial magnetic stimulation (TMS) parameters. METHODS: Ten patients with JME and 10 normal subjects underwent partial sleep deprivation. Motor threshold (MT), motor evoked potential amplitude (MEP), and silent period (SP) were recorded from the thenar eminence (TE) muscles. Short latency intracortical inhibition (SICI) and short latency intracortical facilitation (SICF) were studied using paired magnetic stimulation. TMS was performed before and after sleep deprivation; EEG and TMS were performed simultaneously. RESULTS: In patients with JME, sleep deprivation induced a significant decrease in SICI and an increase in SICF, which was associated with increased paroxysmal activity. A significant decrease in the MT was observed. No significant changes in any TMS parameters were noted in normal subjects after sleep deprivation. The F wave was unchanged by sleep deprivation in both control subjects and in patients with JME. CONCLUSIONS: In patients with JME, sleep deprivation produces increases in corticospinal excitability in motor areas as measured by different TMS parameters.

COMMENTARY

Sleep deprivation is increasingly recognized as an important seizure precipitant, and its relationship to epilepsy was reviewed previously in *Epilepsy Currents* (1). In a prospective survey of 400 patients with epilepsy, Frucht and colleagues found that 62% reported at least one seizure precipitant (2). Stress was the most commonly reported precipitant and occurred in 30% of patients. However, sleep deprivation was the second most common precipitant overall, reported by 18% of patients. Sleep deprivation was reported as a seizure precipitant most frequently in those with idiopathic generalized epilepsies. Others have reported that sleep deprivation is a precipitant in 77% of patients with juvenile myoclonic epilepsy (JME) (3). Thus, sleep deprivation is more than a casual precipitant and has a differentially strong influence on patients with JME.

The studies by Badawy et al. and Manganotti et al. used transcranial magnetic stimulation (TMS) to examine the state of excitability of the motor system. The great value of TMS is that it can noninvasively examine excitability in an awake, intact person; it is applied to the scalp and stimulates a specified area of cortex. The motor response is quantified by measuring the EMG response from the thenar muscles. The state of inhibition can be measured using principles of experimental neurophysiology. A consistent-amplitude, reproducible response can be measured after each stimulus if sufficient time is allowed to elapse between stimulations. Neuronal excitation is followed immediately by inhibition, either from an intrinsic neuronal afterhyperpolarization or because the neuron receives GABAergic inhibitory input. If a second stimulation is delivered during the period when the neuron is inhibited, then there is a decreased response. Paired-pulse inhibition paradigms use the second response to measure the duration and strength of the inhibition. If the response to the second stimulus is as strong as to the first stimulus, then inhibition is impaired.

It is surprising that impaired inhibition was demonstrated so clearly and easily in these experiments, as it has been the subject of such intense scrutiny and controversy in the experimental epilepsy world. Both TMS studies reviewed here reported evidence of impaired inhibition in epilepsy and found the second pulse to be affected at an interpulse interval that potentially

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could result from impaired GABAergic inhibition. However, it is important to note that these TMS experiments only measure the final output of the system and that the simple observation of impaired inhibition on paired-pulse stimulation cannot be taken as direct evidence of impairment of GABAergic interneurons. Instead, it is merely the demonstration of an imbalance of excess excitation and impaired inhibition, possibly representing a final common pathway. If the investigators had given patients a benzodiazepine, it could have revealed whether GABAergic inhibition was specifically affected. The finding of impaired inhibition in epilepsy may seem like a small accomplishment because it has previously been demonstrated in animal models and has been an intense focus of animal research. However, the TMS studies reviewed here are some of the first studies to demonstrate impaired inhibition in humans and particularly in patients with JME.

An important aspect of the study by Badawy et al. is the inclusion of patients with focal epilepsy, for whom the investigators found the same impairment of inhibition as seen in patients with JME, but it appeared only in the hemisphere containing the seizure focus. Thus, the findings may be broadly applicable to epilepsy. It is possible that hyperexcitability represents a general phenomenon in epilepsy, part of the complex milieu needed for epilepsy to occur. However, why would hyperexcitability be present only in the neocortex of one hemisphere?

The findings support some aspects of the known pathophysiology of JME. Although there is no consistent, single pathophysiologic or genetic defect in JME, the most commonly reported mutations affect GABA neurotransmission (e.g., *GABRA1*, encoding the $GABA_A$ $\alpha 1$ subunit), chloride channels (e.g., *CLCN2*), and potassium channels (e.g., *KCNQ3*), among others (4). The fact that the TMS studies support a seemingly consistent defect of inhibition in localization-related and generalized epilepsies suggests that there is indeed a final common pathway of expression, even if there are many different systems affected to arrive there.

Sleep deprivation provides unique insights into epilepsy, but its role in epilepsy also provides insights into the basic biology of sleep deprivation. Sleep deprivation in an animal model can impair neurogenesis (5). It seems reasonable that if sleep deprivation impairs GABAergic inhibition, then it could allow excitatory neurotransmission to go unchecked and contribute to excitotoxicity, at least at the level of the individual neuron. Although speculative, the theory illustrates how this type of active experimental manipulation in human epilepsy can lead to insights about the basic biology of neuronal function.

by Nathan B. Fountain, MD

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RETIGABINE: HAS THE ORPHAN FOUND A HOME?

Randomized, Multicenter, Dose-Ranging Trial of Retigabine for Partial-Onset Seizures. Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM; 205 Study Group. *Neurology* 2007;68(15):1197–1204. OBJECTIVE: To evaluate the efficacy and safety of retigabine 600, 900, and 1,200 mg/day administered three times daily as adjunctive therapy in patients with partial-onset seizures. METHODS: A multicenter, randomized, double-blind, placebo-controlled trial was performed. After an 8-week baseline phase, patients were randomized to a 16-week double-blind treatment period (8-week forced titration and 8-week maintenance) followed by either tapering or entry into an open-label extension study. Primary efficacy was the percentage change from baseline in monthly seizure frequency and compared across treatment arms. Secondary efficacy comparisons included the proportion of patients experiencing 50% reduction in seizure frequency (responder rate), emergence of new seizure types, and physician assessment of global clinical improvement. Safety/tolerability assessments included adverse events (AEs), physical and neurologic examinations, and clinical laboratory evaluations. Efficacy analyses were performed on the intent-to-treat population. RESULTS: Of the 399 randomized patients, 279 (69.9%) completed the double-blind treatment period. The median percent change in monthly total partial seizure frequency from baseline was –23% for 600 mg/day, –29% for 900 mg/day, and –35% for 1,200 mg/day vs –13% for placebo ($p < 0.001$ for overall difference across all treatment arms). Responder rates for retigabine were 23% for 600 mg/day, 32% for 900 mg/day ($p = 0.021$), and 33% for 1,200 mg/day ($p = 0.016$), vs 16% for placebo. The most common treatment-emergent AEs were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia. CONCLUSION: Adjunctive therapy with retigabine is well tolerated and reduces the frequency of partial-onset seizures in a dose-dependent manner.

COMMENTARY

Retigabine is an older agent among the new group of antiepileptic drugs (AEDs)—now involved in its second wave of development. It is the first drug of its class to be studied in clinical trials for any indication (1). Retigabine was initially created and developed by a Former East Germany company and then licensed to a U.S. company for development as an antiepileptic drug in the late 1990s (and finally, to yet another one 3 years ago). During the period of the late 1990s, there was much excitement because retigabine was found to be effective in almost all animal models tested, such as maximal electroshock, pentylenetetrazol, NMDA, picrotoxin-induced seizures, amygdala kindling, and sound-induced seizures in epilepsy-prone rats (1–7). Expectations were high, in light of the animal studies, that it must be a broad spectrum AED.

The phase I trials in normal healthy volunteers were successful, allowing the development of retigabine to proceed and clinical trials for epilepsy were begun. The Porter et al. article reports the first double-blind, randomized clinical trial of retigabine in patients with refractory partial epilepsy. The U.S. drug company that is now working on retigabine as a new AED, initially for partial-onset seizures, appears to be committed to its development as an antiepileptic agent.

What is so interesting about this compound? First of all, it has an unusual mechanism of action, which was well known before clinical trials began, with over 100 preclinical publications providing information on the drug. Retigabine's main mechanism of action is M current modulation—a potassium conductance regulating excitability in neuronal cells (8,9). Its effect occurs by acting on the KCNQ2 and KCNQ3 channels. To date, 5 KCNQ channels have been cloned (2–5,10). Retigabine activates KCNQ2 and KCNQ3. Mutations of these channels have been implicated in human hereditary diseases: benign familial neonatal convulsions (KCNQ2 and KCNQ3) (10), deafness (KCNQ4), and possibly, retinal degeneration (KCNQ5) (7), In addition, retigabine potentiates GABA-evoked channels in high concentrations, causes blockade of 4-aminopyridine–induced stimulation of glutamine release, and stimulates GABA synthesis in rat hippocampus (11).

The drug, as currently formulated, has a short half-life, requiring three times a day dosing in the trials. In the present trial, doses of 600, 900, and 1200 mg were explored for efficacy and tolerability in patients >18 years. Although the drug might be effective in other seizure types, the study only evaluated its effects on partial-onset seizures. The investigators found that retigabine reduced seizures in this refractory group at a rate similar to other new antiepileptic drugs (12). The data indicate that 900 mg probably will be the median dose for this drug, as it produced fewer adverse effects than the 1200-mg dose (17% for the 600 mg arm, 20.2% for the 900 mg arm, and 29.2% for the 1200 mg arm). The adverse effects seem to be dose related and were mainly CNS generated. No hypersensitivity reaction was observed, which is a positive sign.

Currently, there are two ongoing phase III trials, which were designed to try to elucidate issues raised in the Phase II trial concerning efficacy and tolerability, quality of life, and seizure severity. Hopefully, these trials will be available for scrutiny in 1 to 2 years (http://clinicaltrials.gov/).

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Although there are 10 new AEDs available (in addition to one or two more soon to be approved, and others, like retigabine, in clinical trials) as well as treatment options, such as vagus nerve stimulation and epilepsy surgery, an unacceptable number of patients continue to live with refractory seizures. It is interesting to contemplate why this is so. Why is it that drugs with widely different mechanisms of action produce similar results in clinical trials (10); and why are some drugs so effective in animal models of epilepsy and then only moderately effective in humans, such as evidenced in the Phase II trial by Porter and colleagues?

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To Treat or Not to Treat. . .Is It Still the Question?

Treatment of the First Tonic–Clonic Seizure Does Not Affect Long-Term Remission of Epilepsy. Leone MA, Solari A, Beghi E; FIRST Group. *Neurology* 2006;67(12):2227–2229. We followed 419 patients with a first, unprovoked, primarily or secondarily generalized tonic–clonic seizure, randomized to immediate antiepileptic treatment or to treatment only in the event of seizure recurrence. The probability of achieving a 2-year remission was 72 versus 57% at 3 months, 84 to 79% at 3 years, and 85 to 86% at 10 years (p = NS). The probability of entering 5-year remission was 47 to 40%, 58 to 58%, and 64 to 64% (p = NS). Early treatment does not affect the long-term prognosis of epilepsy.

COMMENTARY

The treatment of a first unprovoked epileptic seizure has been and continues to be one of the issues most often debated in epilepsy. In the first major population-based study carried-out more than 20 years ago, Annegers et al. followed 424 patients after an initial first seizure; they found that the risk of recurrence was 36% by one year, 48% by 3 years, and 56% by 5 years (1). Does treatment after a first seizure alter these statistics? To date, there is a consensus that immediate or delayed treatment after a first seizure does not impact the long-term outcome of the seizure disorder. In contrast, immediate treatment prolongs the time to a first breakthrough seizure and increases the percentage of patients that reach an earlier 2-year remission. These conclusions were obtained from one single-center study (2) and four multicenter, randomized studies (one of which is an earlier study of the article reviewed here) that included both children, aged 2 years and older, and adults, including elderly people aged 60 years and older. (3–5).

Two of these studies, known as the First Seizure Trial Group or FIRST studies, included 397 children and adults.

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Among the 204 treated patients, 36 (17.7%) had a breakthrough seizure, while seizures occurred in 75 (39%) of untreated patients, yielding a cumulative risk of seizure recurrence at 24 months of 25 and 51%, respectively (3). However, by 4 years the chance of 2-year remission was of 72 and 67%, respectively, and by 10 years, it was almost identical between the two groups (86 and 85%, respectively) (4). In another study, known as the Multi-Centre Study of Early Epilepsy and Single Seizures or MESS study, patients were randomized to immediate or delayed treatment after a first unprovoked seizure, if the clinician and patients were not sure whether to start treatment (5). Among the 722 patients randomized to immediate treatment 64% achieved an immediate 2-year remission, while this was the case in 52% of patients for whom treatment was delayed. Yet, by 5 (92% in both groups) and 8 years (96 and 95%, respectively) the chance of 2-year remission was almost identical. Furthermore, there was no difference in quality of life between patients who received immediate or delayed treatment.

Yet, while these data may have practical implications for the long-term outcome of patients, they do not provide clinicians with the tools to decide whether to start patients on antiepileptic drugs (AEDs) after a first seizure, since an increased risk of an earlier breakthrough seizure may have negative implications in the life of many patients (e.g., increased risk of self-harm, delay in recovering driving privileges, etc.). Fortunately, several studies have reached a consensus on the variables that increase the risk of seizure recurrence, and these were summarized in a recent review by Haut et al. (6). They include: (1) seizure-type, (2) etiology, (3) EEG data, and (4) sleep state at time of the first seizure. Most of the controversy surrounds the treatment of an initial generalized tonic–clonic seizure, as complex partial seizures are typically associated with an increased risk of recurrent seizures, while myoclonic and absence seizures have already recurred (often for a protracted time period) by the time their existence is brought to medical attention.

An initial remote symptomatic seizure is more likely to be associated with an increased recurrence risk than a cryptogenic seizure, both in pediatric and adult patients. Furthermore, a first unprovoked seizure in which the EEG reveals generalized epileptiform discharges consistent with idiopathic epilepsy is also predictive of an increased recurrence risk and in fact, is comparable to that of remote symptomatic seizures. These two forms of epilepsy differ with respect to their long-term prognosis: idiopathic seizures are likely to enter an early and long-term remission, while remote symptomatic seizures are more likely to have multiple recurrences and are less likely to achieve a long-term remission. Of note, the duration of the first seizure (e.g., status epilepticus as the initial seizure) or a cluster of initial seizures are not predictive of increased recurrence risk in children, but this finding has not been reproduced in adults. Also, children with status epilepticus as the initial ictal event have an increased risk of status in case of recurrence.

Abnormal EEG findings in adults and children are associated with an increased risk of seizure recurrence. In reviewing the literature, Haut et al. conclude that any electrographic abnormality is sufficient to be considered an increased risk of seizure recurrence in children, while in adults, generalized epileptiform discharges are the only pattern with definite risk (the significance of other abnormalities is still being debated) (5). In addition, studies have clearly established a higher recurrence risk when the first seizure occurs during sleep. In children, this association is significant whether sleep is during day or nighttime, while only the latter applies to adults.

The choice of AED depends not only on the type of epileptic seizure and suspected syndrome but must factor in the age, gender, concomitant medication, and comorbid medical, cognitive, psychiatric, or neurologic disorders of the patient. Clearly, the practice of an intravenous load of phenytoin is proving unnecessary in a large majority of patients with new-onset seizures. Furthermore, studies of patients with new-onset epilepsy have shown that AEDs that require a slow titration (e.g., lamotrigine, topiramate) confer comparable protection to those AEDs with more rapid titration rates (e.g., carbamazepine, phenytoin). In a recent study of patients with new-onset partial and idiopathic or unclassified generalized epilepsy (i.e., the Standard and New Antiepileptic Drugs or SANAD Study), patients were randomized to carbamazepine, lamotrigine, topiramate, and gabapentin for the treatment of partial seizures and to valproic acid, lamotrigine, and topiramate for generalized epilepsy (7,8). In patients with partial seizures, lamotrigine was found to be significantly better for time to treatment failure (either because of lack of efficacy or poor tolerability) than the other three AEDs, while lamotrigine and carbamazepine were comparable for time to 12-month seizure remission. For patients with generalized epilepsy, valproic acid was found to be better tolerated than topiramate and more efficacious than lamotrigine.

How long should patients remain on medication? Seizure recurrence after discontinuation of AEDs has been studied by the Medical Research Council of the United Kingdom in 1013 patients who were randomized to slow taper or continued treatment under double-blind, placebo-controlled conditions (9). Seizure relapse occurred in 22% of patients who remained on medication and 44% of those who discontinued the AED. The variables associated with seizure recurrence included: (1) a long history of seizures before remission, (2) more than one seizure type, (3) presence of structural lesion, (4) abnormal neurologic exam, (5) presence of learning disabilities, (6) relapse following prior remission, and (7) juvenile myoclonic epilepsy. In the absence of these variables, AEDs can be discontinued in children after entering a 2-year seizure-free remission, while in adults, a 4-year seizure-free remission is typically required. In summary,

treatment of a first seizure has an impact on the recurrence risk over a short but not a long-time period. Thus, in the end, there is "the good epilepsy" and "the bad epilepsy." The former will respond to most appropriate AED, which eventually may be discontinued; the latter will fail to yield seizure remission with any AED.

by Andres M. Kanner, MD

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Hippocampal Cell Loss in Posttraumatic Human Epilepsy

Hippocampal Cell Loss in Posttraumatic Human Epilepsy. Swartz BE, Houser CR, Tomiyasu U, Walsh GO, DeSalles A, Rich JR, Delgado-Escueta A. *Epilepsia* 2006;47(8): 1373–1382. *Purpose:* We performed this study to determine whether significant head trauma in human adults can result in hippocampal cell loss, particularly in hilar (polymorph) and CA3 neurons, similar to that observed in animal models of traumatic brain injury. We examined the incidence of hippocampal pathology and its relation to temporal neocortical pathology, neuronal reorganization, and other variables. *Methods:* Twenty-one of 200 sequential temporal lobectomies had only trauma as a risk factor for epilepsy. Tissue specimens from temporal neocortex and hippocampus were stained with glial fibrillary acidic protein (GFAP) and hematoxylin and eosin (H&E). Eleven hippocampal specimens had additional analysis of neuronal distributions by using cresyl violet and immunolabeling of a neuron-specific nuclear protein. *Results:* The median age at onset of trauma was 19 years, the median time between trauma and onset of seizures was 2 years, and the median epilepsy duration was 16 years. The length of the latent period was inversely related to the age at the time of trauma ($r = 0.75$; Spearman). The neocortex showed gliosis in all specimens, with hemosiderosis ($n = 8$) or heterotopias ($n = 6$) in some, a distribution differing from chance ($p = 0.02$; Fisher). Hippocampal neuronal loss was found in 94% of specimens, and all of these had cell loss in the polymorph (hilar) region of the dentate gyrus. Hilar cell loss ranged from mild, when cell loss was confined to the hilus, to severe, when cell loss extended into CA3 and CA1. Some degree of mossy fiber sprouting was found in the dentate gyrus of all 10 specimens in which it was evaluated. Granule cell dispersion ($n = 4$) was seen only in specimens with moderate to severe neuronal loss. *Conclusions:* Neocortical pathology was universally present after trauma. Neuronal loss in the hilar region was the most consistent finding in the hippocampal formation, similar to that found in the fluid-percussion model of traumatic head injury. These findings support the idea that head trauma can induce hippocampal epilepsy in humans in the absence of other known risk factors.

COMMENTARY

Among patients with temporal lobe epilepsy and mesial temporal sclerosis (MTS), early studies found that any

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initial precipitating injury, including trauma, most commonly had occurred at or before age 5 years (1,2). Subsequently, Diaz-Arrastia et al. reported MTS-compatible MRI abnormalities in 8 of 23 patients (35%) whose trauma occurred after age 10 years; neuropathological studies confirmed MTS in the two patients who underwent temporal lobectomy (3). Meticulously employing sophisticated techniques, Swartz et al. in this article, document hippocampal neuronal loss in 14 of 15 specimens among patients whose trauma occurred principally in adolescence or adulthood (median age of trauma 19 years; range 1 week–38 years).

The mechanisms underlying posttraumatic seizures and neuronal loss are not completely understood. Previously, Babb and Brown found dual pathology in 13% of temporal lobe epilepsy patients, defined as a macroscopic lesion and severe hippocampal neuronal loss (4). Yeh and Privitera postulated that frequent, chronic activation of a primary focus could produce such hippocampal neuronal loss (5). In adult rats, a single fluid percussion injury evoked ipsilateral frontoparietal seizures that evolved to increasing hippocampal seizures over 7 months and were associated with CA1 and CA3 hippocampal atrophy (6). Importantly, a minor percussion to rat dura also may evoke hilar cell loss and an increase in hippocampal excitability (7). Posttraumatic seizure evolution in humans can parallel that of the rat model: early (<1 posttraumatic week) seizures are focal motor and secondarily generalized, while temporal lobe seizures predominate thereafter, with occasional secondary generalization (8). Thus, trauma either leads directly to mesial temporal neuronal loss or to a focal trauma-induced lesion elsewhere in the cortex, which in some currently unknown manner, leads to hippocampal neuronal loss and provokes temporal lobe seizures. One or both of these sequences could account for the described findings.

Several trauma-related processes may produce mesial temporal neuronal loss and gliosis, including hypoxia, if an injury to the respiratory system has occurred; ischemia from hypotension (systolic pressure < 30 mm/Hg for ≥ 15 minutes); increased intracranial pressure that decreases cerebral perfusion; and carotid or vertebral artery dissection from sudden neck extension (9). One or more such factors may have produced or contributed to MTS in the patients studied here, as all patients (according to the inclusion criteria) suffered moderate trauma. Status epilepticus occurs in 10–20% of early seizures (8), and trauma is an etiology in about 4% of child and of adult status epilepticus series (10). Hippocampal neuronal loss is one consequence of human status epilepticus (10) and occurs in kainic acid-, pilocarpine-, and electrical-stimulation–induced status epilepticus experimental models (11). Enquiry into components of the immediate posttrauma period may clarify longer-term pathophysiological mechanisms.

In humans with temporal lobe epilepsy, Mathern et al. found that hippocampal CA4 neuron densities decrease with longer seizure durations but that this inverse correlation became apparent only after 30 years (12). Although recurrent seizures may have contributed to neuronal loss, Mathern concluded that the initial precipitating injury was the principal culprit. However, this late occurring (>30 years) negative correlation suggests that recurrent limbic seizures may further damage the hippocampus. Mouritzen Dam also documented progressive hippocampal loss, particularly in CA3, that correlated with the duration of the seizure disorder, the number of generalized convulsive seizures, and head injury prior to seizure onset; but not with seizure type, history of status epilepticus, or age at first seizure (13). Additionally, rat hippocampal cell loss from electrical stimulation-induced status epilepticus correlated better with duration to sacrifice than with number of spontaneous seizures (14). Clinical and experimental data suggest that one or more of several trauma-related factors may cause hippocampal neuron loss and other MTS components, launching a process that may spontaneously evolve, augmented by any subsequent recurrent seizures.

In 1899, Bratz, in a detailed and accurate description of MTS, indicated involvement of not only the hippocampus but also of the parahippocampal gyrus and adjacent temporal convolutions (15). The importance of this seminal description increases with recent pathophysiological data that suggest a pivotal role for the subiculum and the parahippocampal region in temporal lobe epilepsy (16). In a human study, microelectrode recordings have disclosed epileptiform activity to propagate from the subiculum to the hippocampus (17) and from the entorhinal cortex to the hippocampus in rat slices (18). Hopefully, future physiopathological studies by Swartz and colleagues as well as by other investigators will determine: (a) the extent and distribution of any lesions in patients with posttraumatic epilepsy and (b) the influence of the lesions on propagation pathways of ictal and inter-ictal epileptiform phenomena.

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