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SEIZURE DISORDERS

RISK OF ANTIEPILEPTIC DRUG WITHDRAWAL IN TUBEROUS SCLEROSIS

Of 122 children with tuberous sclerosis complex (TSC) followed at Texas Scottish Rite Hospital for Children, Dallas, TX, 106 (86.9%) had a history of epilepsy. Fifteen of those with epilepsy whose seizures had remitted were followed for a mean of 5 yrs 7 mos (range, 6 mos to 12 yrs 9 mos) after discontinuing antiepileptic drugs (AED). The AED taper period ranged from abrupt withdrawal to 8 mos (mean, 2.3 mos). A retrospective medical record and neuroimaging analysis of the 15 showed that 5 (33.3%) had a relapse of seizures, and AED treatment was restarted. AEDs were subsequently tapered in one of the 5 without a second relapse. The total sustained remission rate was 73.3% (11 of 15), and the absolute relapse rate was 26.7% (4 of 15). Those with sustained remission had mild neurologic findings, a greater likelihood of normal intelligence, normal EEG at time of AED withdrawal, and few cortical and subcortical tubers on neuroimaging. The patients whose seizures relapsed showed a 4:1 girl-boy ratio, and a higher incidence of retardation. The relapse rate was comparable to that of general pediatric epilepsy cases (25% to 31%). The authors conclude that it is reasonable to consider discontinuing AEDs in carefully selected children with TSC and seizure remission of sufficient duration. (Sparagana SP, Delgado MR, Batchelor LL, Roach ES. Seizure remission and antiepileptic drug discontinuation in children with tuberous sclerosis complex. *Arch Neurol* September 2003;60:1286-1289). (Reprints: Steven P Sparagana MD, Texas Scottish Rite Hospital for Children, 2222 Welborn St, Dallas, TX 75219)

COMMENT. Seizures in tuberous sclerosis patients are often refractory to treatment, and discontinuation of AED treatment is usually considered inadvisable. The above study suggests that in carefully selected patients, a successful withdrawal of

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medication may be possible. The remission rate may have been greater if AEDs had been tapered more slowly.

MECHANISMS OF EPILEPSY

The prevailing theories of epileptogenesis are reviewed from the Departments of Neurology, Beth Israel Deaconess Medical Center, Boston, and the University of California San Francisco, CA. The mechanism in absence seizures involves an alteration in thalamocortical circuits which produces a rhythmic cortical activation, leading to abnormal paroxysms of characteristic EEG discharges and absence attacks. The precise abnormality of the circuit is undetermined, but some data suggest that T-type calcium channels or γ -aminobutyric acid (GABA) receptor function are involved. Ethosuximide and valproic acid cause blockade of T-type calcium currents which inhibits the burst mode of thalamic-relay-neuron firing. Benzodiazepines activate an inhibitory GABA receptor on thalamic reticular neurons.

Many epilepsy syndromes are associated with single-gene mutations. Examples include generalized epilepsy with febrile seizures plus, an autosomal dominant genetic syndrome with linkage to chromosome 19q and a mutation in the gene encoding the voltage-gated sodium channel B1 subunit (*SCN1B*). The mutation promotes depolarization and neuronal hyperexcitability. Phenotypically similar families with this syndrome have been identified with mutations in sodium channel subunits SCN1A and SCN2A and the GABA_A receptor subunit, GABRG2. GABRG2 is also linked to childhood absence epilepsy and febrile seizures. Developmental changes in the nervous system have a role in the clinical expression of genetically-determined generalized epilepsy syndromes.

In partial seizure mechanisms, mesial temporal-lobe epilepsy is associated with hippocampal sclerosis and aberrant sprouting of mossy-fiber axons that instigate a recurrent excitatory circuit in dentate granule cells. Other factors include postnatal neurogenesis in the hippocampus, and molecular alterations such as changes in neurotransmitter receptors. Some partial epilepsies (benign rolandic epilepsy) are genetically determined, suggesting the importance of developmental influences.

Newer areas of research include the role of cortical malformations and of glial cells. Heterotopic neurons are found to lack a potassium channel, leading to hyperexcitability, and some have impaired GABA-mediated inhibitory synaptic transmission. Changes in the neuronal microenvironment can lead to epileptogenesis. (Chang BS, Lowenstein DH. Mechanisms of disease. Epilepsy. *N Engl J Med* September 25, 2003;349:1257-1266).

COMMENT. Generalized and partial epilepsy syndromes have different mechanisms. Generalized epilepsies arise from alterations in neuronal networks or from channelopathies. Partial epilepsies are associated with focal lesions, the most common being hippocampal sclerosis. The role of cortical malformations and glial cells is another important area of research. Whereas advances have been made in the control of seizures, the prevention of the development of epilepsy in patients at risk is elusive.

SCN1A mutations were found in 8 of 24 (33%) patients with severe myoclonic epilepsy of infancy (SMEI) and in one of 23 (5%) with infantile spasms, in a study