

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  $\gamma$ -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<sub>A</sub> 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

involving Centers in Australia, UK, and Canada. (Wallace RH, Scheffer IE et al. Neurology 2003;61:765-769). A family history of seizures was noted in 17 (68%) of SMEI patients.

## **PATHOPHYSIOLOGY OF SEIZURES WITH BRAIN TUMORS**

The etiology of tumor-related seizures (TRS) is reviewed from the Karolinska Institute, Stockholm, Sweden, and University of Pennsylvania, Philadelphia. Multiple causes are considered, involving host and tumor factors. Morphological changes (aberrant neuronal migration, alterations in glial gap-junction coupling), alkaline peritumoral pH, and ion level and amino acid changes (abnormal glutaminergic transmission) in peritumoral brain tissue are probable factors in TRS pathophysiology. Several alterations in enzymatic pathways (eg. lactate dehydrogenase, glutamine synthetase) are observed in epileptic and neoplastic tissues. Cytokines, and tumor necrosis factor in particular, have neuromodulatory effects, and are rapidly induced in glial cells following seizures.

The efficacy of antiepileptic drugs (AED) in TRS is poor, and prophylactic use of AEDs in TRS is not generally recommended. TRS mechanisms (morphological changes, altered receptor patterns, and induction of cytokines) are not influenced by most AEDs. An antineoplastic effect of valproic acid (VPA) is under investigation. Overcoming drug-resistance protein activity (glycoprotein P) may improve response of TRS to AEDs. (Schaller B, Ruegg SJ. Brain tumor and seizures: pathophysiology and its implications for treatment revisited. Epilepsia 2003;44:1223-1232). (Reprints: Dr B Schaller, Department of Neuroscience, Karolinska Institute, Retzius vag 8, S-17177 Stockholm, Sweden).

COMMENT. The records of 291 consecutive children treated for intracranial tumor at the Mayo Clinic from 1950-1959 were analyzed with particular attention to those with seizures (Backus RE, Millichap JG. Pediatrics 1962;29:978-984). Seizures occurred in 17% of the total group – in 25% of patients with supratentorial tumors and in 12% of those with infratentorial tumors. Seizures were the initial symptom in 15% with supratentorial and 1% with infratentorial tumors. Average age at onset of tumor-related seizures was 4.9 years. Diagnosis of supratentorial tumors was delayed for an average of 2 years after the initial seizure, whereas infratentorial tumors were diagnosed within 3 months of the seizure onset. Seizures were more common with slowly growing astrocytomas (67% incidence) than with grades 3 and 4 gliomas (10%). Increased intracranial pressure was present with the first seizure in 79% of infratentorial tumors compared to only 20% of supratentorial tumors.

In a study of 560 patients with supratentorial brain tumor at Walton Hospital, Liverpool, UK, a seizure was the first symptom in 164 (30%). (Smith DF et al. J Neurosurg and Psychiatry 1991;54:915-920). Patients presenting with epilepsy were diagnosed late (mean, 28 months cf 4 months with other symptoms) but had a longer survival (37 months) than those with other symptoms (6 months survival). They were more likely to have a normal neurologic exam and a low-grade tumor. Increasing age at tumor diagnosis, focal neurologic signs, an enhancing CT lesion, surgical biopsy, and male sex were significant independent variables adversely affecting prognosis. Primary IC tumors presenting with epilepsy were relatively benign. They were less likely to receive radiotherapy or biopsy, but more likely to undergo resective surgery. Early resective