IS EPILEPSY A PROGRESSIVE DISEASE?

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The concept that 'seizures beget seizures,' was first suggested by Gowers in the 19th century. Clear clinical evidence for the progression of epilepsy is difficult to find, in part due to the fluctuating course shown by many patients. However, suggestive supporting evidence comes from epidemiological studies showing that the risk of occurrence for subsequent seizures increases with increasing seizure number. Some data suggest that seizure frequency or 'density' rather than absolute number, as well as epilepsy syndrome, predict prognosis. This suggests that the underlying severity of the epilepsy, rather than individual seizures, has the most important effect. Some but not all forms of epilepsy might be 'progressive.'

Progressive neuropsychological impairment has been well documented, particularly in patients with temporal lobe epilepsy, and may be related to seizure frequency and severity.
A substantial number of patients with good initial AED response cease to respond. Tolerance to benzodiazepines is a well-known phenomenon, but some data suggest that it may occur for other AEDs as well. Potential mechanisms of tolerance include neurotransmitter receptor, and neuronal membrane ion channel conformational changes (the latter reported for carbamazepine). Alterations in benzodiazepine allosteric interactions with binding sites on the GABA receptor have been reported. In experimental models, a decreased response to vigabatrin may be due to decreased GABA synthesis caused by feedback inhibition.

Multiple Drug Transporters, particularly the p-glycoproteins, may play a role, although data are conflicting. The proteins pump lipophilic drugs and other xenobiotics out of cells, and have been shown to lead to cancer chemotherapy resistance. Some studies suggest they may be over expressed in human epileptic tissue, particularly from patients with TLE; there is an unreplicated link between MDR gene polymorphisms and human AED resistance.

Imaging studies in patients with mesial temporal sclerosis and other forms of temporal lobe epilepsy in particular show progressive hippocampal atrophy, hypometabolism on fluorodeoxyglucose positron emission tomography and progressive reduction of the ration of N-acetyl aspartate to creatinine plus choline on magnetic resonance spectroscopy. Epilepsy duration seems to be the most important factor, but seizure frequency, and generalized tonic-clonic seizures number, may have an effect as well. Patients whose seizures are well-controlled may have less volume reduction on serial scans than those with persistent seizures. However, volume reduction was also present in some children with only infrequent clinical seizures, and one study suggested that the 'seizure burden' before diagnosis and first MRI scan might play a role. In a community-based longitudinal study, significant atrophy occurred over three years in 17.5% of patients with epilepsy (including temporal lobe, extra-temporal lobe localization-related, and generalized syndromes), compared with 6.7% of control subjects.

The accumulating evidence of progression in at least some forms of epilepsy suggests the possibility of an underlying persistent pathophysiological process. HHV-6 is a beta herpesvirus that reactivates in immunosuppressed and critically ill patients. There are two known variants of HHV-6 termed HHV-6A and B that have different cell tropisms and disease associations. HHV-6B is found largely in roseola, febrile illnesses and immunocompromised transplant patients. HHV-6A has been found primarily in patients with lymphoproliferative disease, AIDS, multiple sclerosis, and immunocompromised patients with CNS disease, and a subset of patients with complex febrile seizures. Preliminary epidemiological data from a multicenter trial have suggested that patients with febrile status epilepticus are more likely than controls to have recent HHV-6B infection. Current studies are investigating the development of mesial temporal lobe epilepsy (MTLE) in this patient group. Interest in the association of HHV-6B in mesial temporal lobe epilepsy was heightened with the publication of findings by investigators at the NINDS that HHV-6B was found at pathogenic levels in the astrocytes of the hippocampus and temporal lobe in 50-60 % of patients with MTLE but not other epilepsy patients, suggesting a possible role of HHV-6 in the development of MTLE. Primary astrocyte cultures infected in vitro with HHV-6 showed a marked decrease in glutamate transporter EAAT-2 expression, suggesting a mechanism for hippocampal injury.

If persistent viral infection in mesial temporal lobe epilepsy is confirmed by further studies, new therapeutic approaches, including antiviral therapy, may be considered for patients with intractable epilepsy.