# Epilepsy

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The commonly used unofficial definition of epilepsy has been "two or more unprovoked seizures at least 24 hours apart." In 2014, the International League Against Epilepsy (ILAE) published a new diagnostic criteria to establish the beginning and end of epilepsy, introduced the paper by Fisher et al. A practical clinical definition of epilepsy, which has provided rational basis for earlier diagnosis of epilepsy in patients presenting with a single seizure. The document also introduces the notion of 'resolved epilepsy', when a person has outgrown an age-dependent syndrome or has been seizure-free for 10 years, the last 5 off of anti-seizure medicines. The broad acceptance of the revised definition will provides a common framework for research studies, as well as for application in clinical practice.

A widely accepted hypothesis in partial epilepsy holds that there is a seizure-free, pre-epileptic state, termed the "latent period", between a brain insult. The relationship between prolonged febrile seizures and the subsequent development of hippocampal sclerosis (HS) and temporal lobe epilepsy has been a matter of great controversy. A landmark prospective multicenter study (FEBSTAT) by Lewis et al. demonstrated that febrile status epilepticus can result in acute hippocampal injury, often evolving to hippocampal sclerosis that is visible on MRI.

The etiology of epilepsy was formerly regarded as unknown in about three-quarters of patients; Many forms of epilepsy have long been suspected to have a genetic background, and improvements in sequencing technology have now enabled detailed dissection of their genetic basis. A meta-analysis of large international collaborative phenotype-genotype data sets (ILAE Consortium on Complex Epilepsies) identified certain loci can broadly affect susceptibility to the development of epilepsy. The epilepsies are a clinically heterogeneous group. The study in all-epilepsy cohort identified two risk loci; at 2q24.3, implicating SCN1A, and at 4p15.1harbouring PCDH7, which encodes a protocadherin protein not previously implicated in epilepsy. Risk locus for genetic generalized epilepsy was at 2p16.1, implicating VRK2 or FANCL, but no significant associations were found for focal epilepsy.

Another advance in genetics of epilepsy is related to the somatic mutations of brain cortical malformations. A genetic etiology is not synonymous with generalized epilepsy, many focal epilepsies have a known genetic cause. Somatic mutation result in two or more populations of cells with distinct genotypes in the same individual. Recent examples include somatic mutations in MTOR, PICK3CA, DCX, LIS1, FLNA and TUBB2B in the patients with cortical malformation.

With rapid progress of genetics and basic neuroscience in this field, there is increasing possibilities for development of antiepileptogenic drugs and novel therapeutic challenges. These cases include individuals with KCNT1 mutations treated with quinidine, KCNQ2 mutations treated with ezogabine (retigabine), GRIN2A mutations treated

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with memantine, mTORopathies treated with everolimus and cannabinoids(medical marijuanas) in children with severe epilepsy. These drugs are increasingly tried in specific patient groups with severe refractory epilepsies for their relevant molecular mechanisms of action against epilepsy.

Important paper in clinical practices is the study on the effects of breastfeeding in children of women taking antiepileptic drugs. Although strong evidence exists that fetal exposure to some AEDs is associated with reduced cognitive abilities in children, harmful effect of breastfeeding during maternal AED therapy to child remains controversial. Meador et al. noted breastfed children exhibited higher IQ and enhanced verbal abilities at age 6 years compared with non-breastfed children.

Recent advance in conventional AED treatment is the development of IV formulation of carbamazepine solubilized in a cycldextrin matrix. Pooled analysis of two open-label studies (phase I and phase III) with epilepsy on stable dosage of oral CBZ (1200-2000mg/day) showed that tolerability profile of IV carbamazepine (70% of oral daily dose, every 6hr) was similar among the different infusion durations (2- to 5-, 15-, or 30-min), and no clinically relevant concerns were identified. An IV carbamazepine formulation would fulfill an important treatment need for patients who have achieved seizure control with oral carbamazepine but for whom oral administration is temporarily not feasible. The New Drug Application (NDA) for this product is currently under review by the FDA.