Epilepsy

Epilepsy is defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause ***(ILAE, 1993)***. Multiple seizures occurring in a 24-hour period or an episode of status epilepticus (SE) are considered a single event. Individuals who have had only febrile seizures or only neonatal seizures (seizures in the first 30 days of life), and people with acute symptomatic seizures, (seizures associated with acute systemic illness, intoxication, substance abuse or withdrawal, or acute neurological insults), and individuals with a single unprovoked seizure, are excluded from this category ***(ILAE, 1993)***.

Epilepsy is a disorder characterized by chronically recurring seizures without clear precipitants. The age-adjusted prevalence of epilepsy is in the range of 4 to 10 per 1000 people in most locations ***(Sander, 2003; Forsgren et al., 2005)***. The burden associated with epilepsy is great, both for the individual with epilepsy and for society at large. Epilepsy can negatively impact cognitive function, is a source of social stigma and legal marginalization, causes increased mortality, economically contributes 0.5% of the global burden of disease, and is associated with an increased risk of psychiatric disorder ***(de Boer et al., 2008)***.

Defining intractable epilepsy is essential not only to identify up to 40% of patients refractory to pharmacological management, but also to facilitate selection and comparison of such patients for research purposes. The ideal definition still eludes us. Multiple factors including number of antiepileptic drug (AED) failures, seizure frequency and duration of unresponsiveness, etiology, and epilepsy syndromes are considered in formulating the definition of pharmaco-resistant epilepsy. Most definitions used in the literature agree on the number of AED failures, which seem to be 2 or 3, however, the seizure frequency and time factor are varied. ***(Sinha and Siddiqui, 2011)***.

The International League Against Epilepsy proposed a definition of drug-resistant epilepsy as a failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules. This for now, could provide an operational definition for clinical and research settings. However, with emergence of new data and novel treatments the criteria for intractability may change ***(Sinha and Siddiqui, 2011)***.

Epidemiology:

Pooya and Sperling, (2008), stated that about 50 million people suffer from epilepsy, of whom 80% live in resource poor

countries ***(Winkler et al., 2007)***. The incidence of epilepsy in low-income countries may be as high as 190 per 100,000 people ***(Placencia et al., 1994)***.

Consequently, in the context of the large and rapidly increasing populations in these countries, epilepsy is a significant health and socioeconomic burden. However, of about 40 million people with epilepsy, who live in developing countries, perhaps around 90% do not receive appropriate treatment ***(Scott et al., 2001)***. As a consequence, they experience morbidity related to seizures and the psychosocial consequences of stigma, discrimination, and underemployment ***(Perucca, 2007)***.

On the other hand, although mortality among people with epilepsy is high, the chances of remission are also high and therefore, the probability that such people being young, fully contributing members of society is higher than people with coronary artery disease, where the afflicted population is more often elderly ***(Scott et al., 2001)***.

Around 65% of newly diagnosed epilepsy patients will have a good response to the antiepileptic drugs (AEDs). However, about 35% of patients will have incompletely controlled epilepsy ***(Kwan and Brodie, 2000)***. Focal epilepsies and symptomatic generalized epilepsies are less likely to be

controlled easily by medication than the idiopathic generalized epilepsies. For practical purposes, a patient may be regarded as having refractory epilepsy when seizure control is not obtained with consecutive trials of two or three well-tolerated AEDs ***(Brodie, 2005)***.

In North America, age-adjusted incidence of epilepsy ranged from 16 per 100,000 person-years ***(Benn et al., 2008)*** to 51 per 100,000 person-years ***(Hauser et al., 1993)***. Prevalence was estimated to be 5.0 ***(Zenteno et al., 2004)*** and 5.2 ***(Wiebe et al., 1999)*** per 1000 in two studies conducted in Canada, while age-adjusted prevalence in Africa ranged from 3.9 per 1000 in Tunisia ***(Romdhane et al., 1993)*** to 13.2 per 1000 in Zambia ***(Birbeck and Kalichi, 2004)***.

In Central and South America, the overall age-adjusted prevalence ranged from 3.7 per 1000 in Argentina ***(Melcon et al., 2007)*** to 22.2 per 1000 in Ecuador ***(Cruz et al., 1985)***. In South America, the lowest age-adjusted prevalence was 3.7 ***(Melcon et al., 2007)***.

Pathogenesis:

Epileiptogenesis:

Epileptogenesis is the process by which a "normal" brain becomes epileptic. Most work on epileptogenesis has focused on

acquired forms of epilepsy, in which there is an inciting event such as injury or prolonged seizure, followed by a clinically latent period during which the brain undergoes repair and reorganization to a hyperexcitable state, succeeded by a clinically epileptic phenotype. Throughout epileptogenesis, modulating factors such as genetics, age, and the inherent structural and functional plasticity of the brain in question help to determine the progression to chronic or refractory epilepsy **(Fig. 1)** ***(Giblin and Blumenfeld, 2010)***.

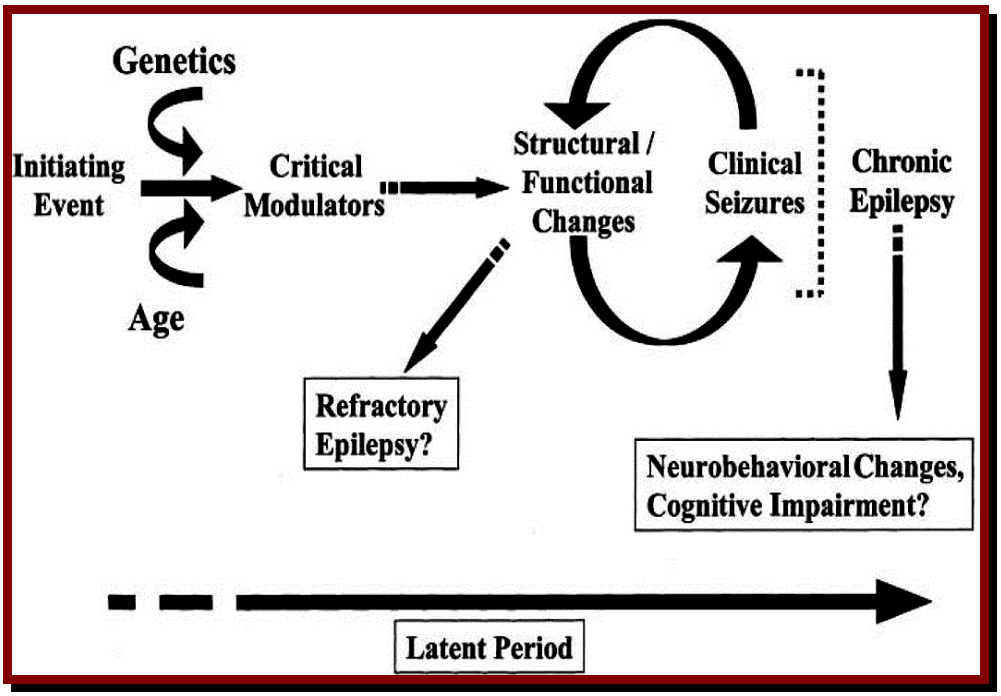

Fig. 1: Schematic of epileptogenesis ***(Giblin and Blumenfeld, 2010)***.

In humans, events that may incite acquired epileptogenesis include traumatic brain injury, stroke, central nervous system

infection, neoplasm, intracerebral hemorrhage, complex febrile seizures, and status epilepticus ***(Shinnar et al., 2000; Herman, 2002)***. One inciting event may be sufficient, or multiple "hits" may be required for the development of epilepsy ***(Dichter, 2009a)***.

Factors that have been shown to modulate progression to epilepsy include family history of seizure, age, gender, existing organic brain disease, and psychiatric comorbidity ***(Hauser and Annegers, 1991; Hesdorffer et al., 2000; Frey, 2003)***. In experimental models, repeated subthreshold electrical stimulation (kindling), drug- or electrical stimulus–induced status epilepticus, prolonged hyperthermia-induced seizures, traumatic brain injury, and ischemia are among the mechanisms used to induce epileptogenesis.

Recent work suggests that a similar process of epileptogenesis may also occur in genetic forms of epilepsy. In such disorders, there is an underlying genetic predisposition that initiates epileptiform events. However, even in genetic forms of epilepsy, recurrent epileptiform events may lead to abnormal activity-dependent plasticity, which can both contribute to further tendency for seizures, and to other adverse chronic changes in the nervous system ***(Massa et al., 2001; Staley et al., 2005; Nicolai et al., 2007)***.

Cellular and Electrical Mechanisms of Epileptogenesis:

As the brain becomes epileptic, a combination of cell loss, increased excitability, and formation of abnormal circuits occurs. Cellular mechanisms of epileptogenesis are numerous and include cell loss, gliosis, increased expression of intermediate-early genes c-fos and c-jun, as well as growth factors, neurogenesis, synaptogenesis, alterations in glutamate and GABA signaling, inflammatory mediators, changes in voltage-gated ion currents, and excitotoxic antibodies ***(Ransom and Blumenfeld, 2007)***.

In tandem with the cellular changes of epileptogenesis, there are often electroencephalographic (EEG) changes that occur prior to the full development of epilepsy. These nonseizure EEG changes include interictal spikes, which have been shown to occur immediately after brain injury and prior to the first spontaneous seizure ***(Hellier et al., 1999)***, and which are correlated with spontaneous seizures ***(Sundaram et al., 1999)***. Interictal spikes are transient EEG discharges that occur when paroxysmal depolarizations of cortical neuron membrane potential cause a series of action potentials ***(Matsumoto and Marsan, 1964)***.

Spikes have been hypothesized to be both the result of cellular changes during epileptogenesis and the cause of further

cellular changes, serving to reinforce and maintain epileptogenesis ***(Staley et al., 2005; Staley and Dudek, 2006)***. Brain injury and subsequent disinhibition of dentate granule cells, as seen after epileptogenic events, have been shown to produce spikes ***(Prince, 1968; Kobayashi and Buckmaster, 2003)***. In turn, spiking has been causally associated with some of the processes that underlie epileptogenesis. Spiking has been shown to cause long-term potentiation (LTP) ***(Bains et al., 1999)***, drive activity-dependent gene expression ***(Rakhade et al., 2007)***, and provide synchronous activity that may guide axon growth ***(Hanson and Landmesser, 2004)***.

Epileptogenesis as a Critical Period:

In development, there are certain transient periods of time, known as "critical periods", during which particular stimuli cause irreversible changes in brain function. During critical periods, certain neural circuits have increased plasticity and undergo experience-dependent architectural remodeling, resulting in a highly stable pattern of connectivity ***(Knudsen, 2004)***.

Critical periods have been shown to occur in learning processes such as filial imprinting ***(Horn, 2004)***, ocular representation in the visual cortex ***(Wiesel and Hubel, 1965)***, and language acquisition ***(Arshavsky, 2009)***. While critical periods are generally conceptualized as times of developmentally normal

learning, they also represent an increased susceptibility to abnormal learning. There are certain sensitive time windows during development when an initial insult is more likely to initiate epileptogenesis, and in genetic forms of epilepsy, age of seizure onset is often stereotyped ***(Ben-Ari and Holmes, 2006)***.

This likely represents a specific developmental milieu, which renders the brain more susceptible to abnormal learning and formation of aberrant neural circuitry. Likewise, in older animals, the period soon after epileptogenic insult represents a time of increased plasticity when aberrant neuronal networks that serve to facilitate seizures are formed and strengthened ***(Bragin et al., 2000)***.

By intervening to block the cellular and electrical mechanisms at work during the critical period for epileptogenesis, it may be possible to prevent epilepsy.

Post-traumatic Epilepsy:

Epilepsy after head injury is a major concern in humans. Posttraumatic epilepsy (PTE) occurs in 16.7% of patients with severe head injury ***(Annegers et al., 1998)***, and soldiers with missile head injuries have a 50% incidence of epilepsy ***(Lowenstein, 2009)***. Animal models of PTE include neocortical islands, fluid percussion, controlled cortical impact (CCI), iron

injection, weight drop, and penetrating ballistic-like injury ***(Pitkanen et al., 2009)***.

In the neocortical island model, an area of neocortex with intact blood supply is isolated both via transcortical lesioning and white matter undercutting ***(Echlin and Battista, 1963)***. Lesioning is succeeded by a 1- to 2-week latency period, followed by spontaneous seizures ***(Hoffman et al., 1994)***. In the fluid percussion model, a single pressure pulse on the dura replicates closed-head injury without cortical damage ***(McIntosh et al., 2004)***.

Electrographic, subclinical seizures develop as early as 2 weeks after trauma in some animals, and clinical seizures are seen in a subset of the animals at 7 weeks to 1 year ***(D'Ambrosio et al., 2004; Kharatishvili et al., 2006)***. The CCI model involves contusion to intact dura with a pneumatic device, allowing for modulation of injury depth ***(Lighthall 1988)***. Clinical seizures are seen after 6 to 10 weeks in 20% to 36% of animals ***(Hunt et al., 2009)***.

Mechanisms:

Pathogenesis of PTE can be divided into primary damage, which incites immediate molecular and ionic changes, and secondary damage, including gliosis, axonal injury + sprouting,

neurodegeneration + neurogenesis, and vascular damage + angiogenesis ***(Pitkanen et al., 2009)***. In the neocortical island model, changes in gene expression have been seen within the first 24 hours, including increased levels of neuronal activity–related pentraxin (Narp) ***(Song et al., 2002)***, which has been shown to promote excitatory syaptogenesis ***(O'Brien et al., 1998)*** and neurite outgrowth ***(Tsui et al., 1996)***. At 3 days postlesioning, there is increased immunoreactivity of growth associated protein 43 (GAP43), and at 3 weeks, there is increased 68-kDa neurofilament immunoreactivity ***(Prince et al., 2009)***.

Chronically, larger axonal arbors and increased synaptic bouton density in layer V pyramidal neurons have been seen ***(Salin et al., 1995)***. In the fluid percussion model, there is reactive gliosis ***(Felberg et al., 1999)***, which has been correlated with epilepsy ***(D'Ambrosio et al., 2004)***. Hippocampal sclerosis has been observed after fluid percussion ***(Hicks et al., 1996)***, along with increased hippocampal BDNF and TrkB, and decreased hippocampal neurotrophin-3 ***(Hicks et al., 1999)***.

Animals that exhibited seizures after CCI exhibited reduction in paired-pulse ratios and increased spontaneous and hilar-evoked epileptiform activity in the dentate gyrus. These animals also had mossy fiber sprouting ipsilateral to the CCI ***(Hunt et al., 2009)***.

Recently, it has been hypothesized that disruption of the blood-brain barrier (BBB) plays a primary role in both posttraumatic brain injury and poststatus epilepticus epileptogenesis ***(Friedman et al., 2009)***. The degree of BBB permeability after status has been correlated with seizure frequency, and opening the BBB with mannitol was found to increase seizure frequency in epileptic rats ***(van Vliet et al., 2007)***.

It has been theorized that BBB disruption induces epileptogenesis by allowing albumin leak, causing astrocyte activation via binding to the transforming growth factor-beta (TGF-β) receptor and subsequent release of inflammatory mediators ***(Vezzani et al., 2008)*** and impairment of buffering capacity and glutamate metabolism ***(Friedman et al., 2009)***. Supporting this hypothesis, TGF-β receptor activation with TGF-β1 has been shown to be sufficient for epileptiform activity and results in similar gene expression patterns to BBB breakdown or albumin exposure ***(Cacheaux et al., 2009)***.

C. Epileptogenesis in Primary Generalized Epilepsy:

Although primary generalized epilepsy by definition does not have a clear-cut inciting event, as do the aforementioned models of acquired epilepsy, certain animal models of primary

generalized epilepsy do have a defined period of epileptogenesis, when abnormal cellular changes occur in association with seizure development. In the WAG/Rij rat, a model of absence epilepsy, the period of seizure development occurs between the ages of 2 to 4 months. On EEG, spike-wave discharges (SWDs) appear and increase in frequency during this time, and there is a corresponding upregulation of cortical voltage-gated sodium channels Nav 1.1 and 1.6 within the facial somatosensory cortex ***(Klein et al., 2004)***.

This upregulation of cortical Nav 1.1 and 1.6 may be a cellular mechanism of epileptogenesis in this model, with self-reinforcing activity-dependent changes similar to those seen in kindling ***(Blumenfeld et al., 2009)***. Voltage-gated sodium channels (VGSCs) determine neuronal excitability and contribute to burst firing, which plays an important role in SWD generation ***(Blumenfeld and McCormick 2000)***. Supporting the epileptogenic nature of this local VGSC increase, the area of seizure onset in the WAG/Rij rats has also been localized to the facial region of the somatosensory cortex ***(Meeren et al., 2002)***.

Also in the somatosensory cortex at greater than 2 months, there is a decrease in HCN1 protein expression and a corresponding reduction in the h current density and rate of activation, which would contribute to hyper-excitability ***(Strauss***

et al., 2004). Like the changes in sodium channel expression, this HCN1 reduction and resulting hyperexcitability is most likely an activity-dependent, self-reinforcing process. In organotypic hippocampal slice cultures, HCN1 expression was decreased by kainate-induced seizure-like activity via AMPA receptor-mediated calcium influx and subsequent calcium/calmodulin-dependent protein kinase II activation ***(Richichi et al., 2008)***. Other changes in ion channel expression and in dendritic morphology have also been described in WAG/Rij rats compared to nonepileptic controls ***(Karpova et al., 2005)***.

In terms of imaging markers of epileptogenesis, 8-month-old adult WAG/Rij rats had reduced fractional anisotropy with increased perpendicular diffusivity in the anterior corpus callosum, indicating reduced myelin and/or axon fiber density in pathways connecting epileptic somtosensory cortex. These changes were not seen in WAG/Rij rats prior to seizure onset at 1.7 months of age ***(Chahboune et al., 2009)***.

Given the defined cellular and EEG changes occurring in the WAG/Rij rats between 2 and 4 months and imaging changes between 1.7 and 8 months, this represents a critical period of epileptogenesis during which blockade of either the cellular or electrical mechanisms of epileptogenesis could prevent development of the epileptic phenotype.

Cardinal Semiology of Temporal Lobe Seizures:

Prodrome:

Some patients experience preictal events, which may be helpful in predicting a coming seizure. Prodromes may last several minutes, hours, or, occasionally, even days. Examples of prodromes include headache, personality change, irritability, anxiety, or nervousness. These phenomena should not be confused with seizure onset. Often, prodromes are recognized by family and friends but, not by the patient (especially changes such as irritability or exhilaration) ***(Blair, 2012)***.

Aura:

Auras (from the Latin for breeze, Greek for air) are in fact simple partial seizures and can occur in isolation but occur in the majority of patients at the onset of a CPS. They can last from seconds to a long as 1-2 minutes before consciousness is lost. The types of auras patients report may correlate with the site of seizure onset. Some authors have questioned the localizing value of the aura as a marker of ictal origin in CPSs ***(Janati et al., 1990)***.

Many authors, however, have noted a close association of some sensory auras with temporal lobe seizures. Examples include viscerosensory symptoms such as a rising epigastric