Epilepsy: Pathophysiology and Associated Comorbidities

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Abstract

Epilepsy is a complex disease with diverse clinical characteristics that preclude a singular mechanism. One way to gain insight into potential mechanisms is to reduce the features of epilepsy to its basic components: seizures, epileptogenesis, and the state of recurrent unprovoked seizures that define epilepsy itself. Epilepsy is one of the most common and disabling neurologic conditions, yet we have an incomplete understanding of the detailed pathophysiology and, thus, treatment rationale for much of epilepsy. Comorbid health conditions are common among people with epilepsy. Proposed explanations for this association include the possibility that first, epilepsy (including its treatment) causes the comorbid condition; second, the comorbid condition (including its treatment) causes epilepsy; or third, a common pathogenic mechanism mediates the co-occurrence of epilepsy and the comorbid condition. It is unlikely that a single explanation will suffice for all of the epilepsy comorbid conditions. Determining the basis of the association between epilepsy and its comorbid conditions has important implications for diagnosis and management. In this paper, we discussed the pathophysiological features and neurobiology of epilepsy also in this issue in the context of common epilepsy comorbid conditions: Stroke, depression, and attention-deficit hyperactivity disorder. Current findings, research limitations, and future directions of research efforts are discussed.

Keywords: Attention deficit hyperactivity disorder, depression, epilepsy, migraine, stroke

Introduction

A “seizure” is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. “Epileptic seizure” is used to distinguish a seizure caused by abnormal neuronal firing from a non-epileptic event, such as a psychogenic seizure. “Epilepsy” is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction.[1] A seizure provoked by a reversible insult (e.g., fever and hypoglycemia) does not fall under the definition of epilepsy because it is a short-lived secondary condition, not a chronic state. “Epilepsy syndrome” refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, electroencephalogram (EEG) findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs). The non-specific term “seizure disorder” should be avoided.

Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per year per 100,000 population.[2]

Much of what we know about epilepsy emerged in the 1800s with the first evaluation of autopsy specimens from individuals with epilepsy. The seminal work of Bouchet and Cazauvieilh in 1825,[3] followed by Sommer[4] and other scientists decades later (for a review see Scharfman and Pedley[5]), suggested profound structural changes to the brain in patients with epilepsy. A new era in epileptology began with neurologists such as Jackson[6,7] in the late 1800s providing suggestions for the ways seizures might occur. In the 1900s, the most important advances were the development of the EEG and the first recordings of the EEG in patients with epilepsy by Gibbs et al.,[8] Jasper et al.,[9] and Penfield and Jasper.[10] In parallel, the breakthroughs in understanding the essential aspects of nerve cell function, from Hodgkin and Huxley[11] to others (for a review Hille[12]), shaped a growing appreciation that epilepsy was a complex disorder that could best be understood through diverse approaches. Today, the combined efforts of clinical and basic research have demonstrated the wealth of potential mechanisms, facilitated by the emergence of the field of neuroscience.
Classification of Seizures and Epilepsy

The most recent international league against epilepsy classification of epileptic seizures and epilepsies (epilepsy syndromes), published in 2010, revises past classifications using terminology and concepts appropriate for the modern era.[13] Seizures are divided into three categories: Generalized, focal (formerly called partial), and epileptic spasms [Figure 1]. Focal seizures originate in neuronal networks limited to part of one cerebral hemisphere. Generalized seizures begin in bilateral distributed neuronal networks. A seizure can begin focally and later generalize. Seizures can originate in the cortex or in subcortical structures. Using a detailed history, EEG findings, and ancillary information, a physician can often categorize the seizure/epilepsy type, after which an appropriate diagnostic evaluation and treatment plan are formulated.

The main subtypes of generalized seizures are absence, generalized tonic–clonic (GTC), myoclonic, and atonic. Absence seizures (formerly called petit mal) involve staring with unresponsiveness to external verbal stimuli, sometimes with eye blinking or head nodding. GTC seizures (formerly called grand mal) consist of bilateral symmetric convulsing movements (stiffening followed by jerking) of all limbs with impairment of consciousness. Myoclonic seizures consist of sudden, brief (“lightning-fast”) movements that are not associated with any obvious disturbance of consciousness. These brief involuntary muscle contractions may affect one or several muscles; therefore, myoclonic seizures can be generalized or focal. Atonic seizures involve the loss of body tone, often resulting in a head drop or fall.

Association of Epilepsy and Associated Comorbid Conditions

Comorbidity refers to the cooccurrence of two conditions with a greater frequency than found in the general population.[14,15] Comorbid conditions are common in people with epilepsy, and their presence has important implications for diagnosis, treatment, medical costs, and quality of life.[16-18] Comorbid conditions in epilepsy are found across the lifespan, and include medical, psychiatric, and cognitive conditions alone or in combination. In 2003, Boro and Haut succinctly summarized the problem of comorbidity in epilepsy: “Nearly every patient with epilepsy will experience a comorbid medical condition at some point during the course of treatment.”[19] Epidemiologic findings are an important source of data concerning the issue of comorbidity in epilepsy. These studies confirm high rates of comorbidity in epilepsy and they include conditions associated with almost every organ system in the body. Six recent large-scale studies, surveying over 1.4 million subjects from different countries, reported that between 26.8% and 84% of epilepsy patients had at least one comorbid medical condition.[20-24] Similarly, seven epidemiological or large-scale studies, including nearly 300,000 people, reported rates of psychiatric comorbidity ranging from 5.9% to 64.1% in epilepsy samples compared with 7–26.8% in non-epilepsy control samples.[25-27] Mood disorders are the most common, but several other psychiatric conditions are also represented. A high incidence of coexisting cognitive impairment, including learning disability and academic underachievement, has been frequently documented.[28] It is also likely that many people with epilepsy, particularly older adults, have more than one comorbid condition[29] [Table 1].

Figure 1: Classification of seizures
Table 1: Comorbid conditions with significantly higher rates in epilepsy than in the general population

<table>
<thead>
<tr>
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<tr>
<td>• Musculoskeletal system disorders</td>
<td>• Gastrointestinal and digestive disorders</td>
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<td>• Respiratory system disorders</td>
<td>• Chronic pain disorders</td>
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<td>• Malignancies</td>
<td>• Cerebrovascular accidents</td>
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<td>• Migraine</td>
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<td>• Arthritis/rheumatism</td>
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<td>Psychiatric</td>
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<td>• Depression</td>
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<td>• Anxiety</td>
<td>• Attention-deficit hyperactivity disorder</td>
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<tr>
<td>• Autism spectrum disorders</td>
<td>• Learning disability</td>
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<tr>
<td>• Intercital dysphoric disorder</td>
<td>• Mental retardation</td>
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<tr>
<td>• Intercital behavior syndrome</td>
<td>• Alzheimer’s disease/dementia</td>
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Multiple causal models have been considered to explain the cooccurrence of epilepsy with other medical, psychiatric, and/or cognitive conditions. The three most common are: First, epilepsy (or its treatment) causes the comorbid condition(s); second, the comorbid condition (or its treatment) leads to epilepsy; or third, a shared underlying mechanism (biological and/or environmental factors) mediates the occurrence of both epilepsy and the comorbid condition(s). The first two possibilities are considered unidirectional models, whereby one condition leads to the occurrence of the other condition. The third possibility suggests that neither condition directly causes the other but instead a third factor may underlie both the epilepsy and its comorbid condition. In these instances, the comorbid rate of occurrence is high in both directions (i.e., epilepsy shows higher incidence of comorbid condition and comorbid condition shows higher incidence of epilepsy) and data indicate that either condition may predate the occurrence of the other.

Table 1 provides examples of comorbid medical, psychiatric, and cognitive disorders reported to be more common in epilepsy than in the general population.

Stroke

It is well-established that strokes can lead to epilepsy (also known as post-stroke epilepsy [PSE]), particularly in the elderly when it is the most common cause of new-onset epilepsy. Several studies, which exclude acute seizures (first 2–4 weeks), indicate that 2–4% of stroke patients develop epilepsy over a period of several months, and people with stroke run a 23-times greater risk of developing seizures within the 1st year post-stroke than those who do not have a stroke. When the number of annual stroke cases in the USA is considered (approximately 600,000), this amounts to a relatively large number of cases of PSE. With PSE, the temporal sequence implicates the stroke as the cause for the onset of epilepsy. Several stroke-related factors, such as severity, location of vascular abnormality, and type of vascular incident, have been shown to affect the occurrence of PSE. Furthermore, among those who develop new-onset seizures in the elderly, cardiovascular abnormalities were quite common. Of interest, the additional risk factors identified for developing PSE include pre-existing dementia, possibly due to dysfunction in the excitatory amino acid pathways, and women appear to be more vulnerable than men.

Depression

The association between epilepsy and depression has been noted since the time of Hippocrates. Intercital depression is the most common psychiatric comorbidity in epilepsy and occurs more frequently in epilepsy than in other neurologic conditions and other chronic non-neurological conditions. Up to recently, depression was viewed as a reaction to epilepsy (e.g., stigma and poor quality of life). Multiple risk factors, including AED treatment, seizure-related characteristics, and social coping and adaptation skills, have been identified in the comorbidity of depression and epilepsy. AEDs are thought to exert a significant impact on mood. They can lead to fatigue, sleep and eating difficulties, slowed thinking, and decreased energy and alertness, all of which are core symptoms of depression. Seizure-related factors implicated in the development of depression include limbic-related seizures (e.g., temporal lobe epilepsy). Left-sided seizure activity, particularly when involving concomitant frontal dysfunction has also been suggested as a risk factor. Psychosocial variables are acknowledged to play an important role in the cooccurrence of epilepsy and depression. Perceived stigma associated with epilepsy also significantly contributes to poor self-esteem, rejection by peers, avoidance of age-appropriate activities, and social isolation in children.

Attention Deficit Hyperactivity Disorder (ADHD)

In 1955, Ounsted was among the first to call attention to the syndrome of hyperkinetic disorder in children with epilepsy, including features of overactivity, distractibility, poor impulse control, and behavior problems. Support for the comorbidity between epilepsy and ADHD comes from national surveys and population-based study and tertiary-care centers. The influence of AEDs is often cited as a potential cause for the observed cooccurrence, and several AED medications can produce the core symptoms of ADHD (e.g., high activity, aggressiveness, and distractibility). However, ADHD has also been reported to predate the first seizure (and AED treatment) in a substantial number of children. The association between epilepsy and ADHD (temporal contiguity) is consistent with the notion of a common underlying pathophysiological mechanism for the two disorders, whereby the order of their appearance
is influenced by either/or both genetic and environmental factors (e.g., perinatal insult and head injury). Common biological mechanisms suggested for the cooccurrence include disruption of lipid metabolism, the norepinephrine system or the dopamine transporter system. In 2007, Hermann found that children with ADHD and new-onset epilepsy showed significantly increased gray matter frontal lobe brain volumes and decreased brainstem volumes compared with children with epilepsy alone.43,44 The presence of comorbid ADHD was also associated with poorer performance on tasks of executive functioning. Genetic mechanisms have also been suggested for this. Animal studies have demonstrated that rats bred to be seizure prone are more likely to display symptoms of ADHD than rats not bred to be seizure prone.45

**Conclusion**

Seizure generation in the normal brain has many potential mechanisms, and this is not surprising in light of the multitude of ways the CNS is designed to balance excitation and inhibition. Epilepsy is comorbid with conditions that span the medical, psychiatric, and cognitive spheres of functions and provides a significant conundrum for diagnosis and treatment. Several conditions (e.g., depression, stroke, and ADHD) are proving to have a complex connection whereby a shared underlying pathogenic mechanism may be responsible for the cooccurrence of epilepsy with these conditions.

**References**

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