Published in final edited form as:
Future Neurol. 2009 September 1; 4(5): 663–668. doi:10.2217/fnl.09.32.

Association of epilepsy and comorbid conditions

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Abstract

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 discuss this issue in the context of five common epilepsy comorbid conditions: bone health and fractures, stroke, depression, migraine and attention-deficit hyperactivity disorder. Current findings, research limitations and future directions of research efforts are discussed.

Keywords

ADHD; bone health; causal models; comorbidity; depression; epilepsy; migraine; risk factors; stroke

Comorbidity refers to the co-occurrence of two conditions with a greater frequency than found in the general population [1,2]. Comorbid conditions are common in people with epilepsy, and their presence has important implications for diagnosis, treatment, medical costs and quality of life [3–5]. 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

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Financial & competing interests disclosure
The authors are supported by grant from National Institutes of Health (NINDS RO1-44531). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

epilepsy will experience a comorbid medical condition at some point during the course of treatment" [6].

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 [2,7–11]. 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 nonepilepsy control samples [7–9,11–14]. 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 [15]. It is also likely that many people with epilepsy, particularly older adults, have more than one comorbid condition [16]. Box 1 provides examples of comorbid medical, psychiatric and cognitive disorders reported to be more common in epilepsy than in the general population.

Box 1

Comorbid conditions with significantly higher rates in epilepsy than in the general population

Medical

- Musculoskeletal system disorders
- Gastrointestinal and digestive disorders
- Respiratory system disorders
- Chronic pain disorders
- Cerebrovascular accidents
- Migraine
- Neoplasia
- Arthritis/rheumatism
- Obesity
- Diabetes
- Infections
- Fractures
- Allergies

Psychiatric

- Depression
- Anxiety
- Autism spectrum disorders
- Interictal dysphoric disorder
- Interictal behavior syndrome
- Psychosis of epilepsy

Cognitive

- Attention-deficit hyperactivity disorder
- Learning disability
- Mental retardation
- Alzheimer's disease/dementia

Multiple causal models have been considered to explain the co-occurrence 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.

In this paper, we consider several common comorbid conditions in epilepsy that illustrate the complex potential relationships that exist between epilepsy and its comorbid conditions. Simple and direct cause–effect relationships may not be sufficient to explain these comorbid associations. Instead, multiple causes that in some instances may include a shared underlying predisposition or pathogenesis may account for the co-occurrence.

Bone health

Bone health problems (e.g., low bone mineral density and osteoporosis) are common among people with epilepsy. Long-term use of anti-epileptic drugs (AEDs) is commonly associated with bone health problems, particularly in women [17]. Cytochrome P450 enzyme-inducing AEDs (e.g., phenytoin, phenobarbital and carbamazepine) are associated with an adverse impact on bone health owing to their effect on vitamin D and resulting calcium deficiency. Other risk markers identified include older age, menopause in women, longer duration of AED use and assisted ambulation. Furthermore, poor bone health may play a role in leading to other comorbid conditions associated with epilepsy (e.g., obesity and depression) by reducing the opportunity for physical activity and/or reducing opportunities for social interaction [18].

Bone fractures occur as much as two-times more frequently in epilepsy than the general population; however, the deficit in bone mineral density does not appear to fully account for the increased risk of fractures [19,20]. Fractures may also be due to the seizures themselves or to falls associated with adverse drug effects (e.g., dizziness and ataxia). For example, convulsions during the seizure may produce a fracture. People with tonic–clonic seizures are at higher risk for fractures than other seizure types. Tonic and atonic seizures consist of a sudden onset of increased muscle tone, which is likely to include falls and increase the likelihood of bone fractures. Thus, the increased incidence of bone fractures in epilepsy appears to be associated with several risk factors.

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

[21]. 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 first year post-stroke than those who do not have a stroke [22,23]. 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 [24]. Furthermore, among those who develop new-onset seizures in the elderly, cardiovascular abnormalities were quite common [21]. 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 [25].

Less appreciated is that several stroke risk factors are found in people with epilepsy prior to the actual stroke. It is not uncommon for people with epilepsy to have multiple stroke risk factors. Population-based surveys document higher rates of hypertension, ischemic heart disease and diabetes in people with epilepsy. Disruption of folate metabolism and concomitant increase in homocysteine have been linked to enzyme-inducing AED medications. Abnormalities in cholesterol levels and lipoprotein homeostasis are also reported. Compared with controls, young adults with epilepsy presented significantly increased carotid artery intima thickness.

Depression

The association between epilepsy and depression has been noted since the time of Hippocrates. Interictal 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 [26]. Until 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 [8]. 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 [27]. 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 [28]. Psychosocial variables are acknowledged to play an important role in the co-occurrence 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 [29].

More recently, empirical evidence indicates that major depression may also be a risk factor for developing epilepsy [27,30]. The temporal sequence of the occurrence of depression and epilepsy goes in either direction. Psychiatric symptoms were found to predate the onset of epilepsy in up to 45% of patients [31–33]. These findings are consistent with the hypothesis that a shared underlying pathophysiological mechanism may form the basis for both conditions. Suggested biochemical factors include decreased serotonin (5HT), noradrenaline (NE), glutamate and GABA, as well as reduced folate metabolism [34,35].

Migraine headaches

There is a long history of investigation into the connection between epilepsy and migraine; however, questions remain regarding the temporal order of their occurrence and the basis for the association. The prevalence of migraine in epilepsy and epilepsy in migraine are increased compared with the general population, particularly in people who experience a visual aura

along with the migraine [3,36]. They co-occur with several of the same conditions, including stroke and depression, and share a set of clinical features, including paroxysmal events, impaired consciousness and focal neurologic signs, and also some common risk factors [37, 38]. In addition, some AED medications are generally considered to be an effective treatment option for migraines, possibly by reducing neuronal instability and hyperexcitability [39].

Shared genetic and physiologic mechanisms that have been identified include brain hyper-excitability originating from cortical depression [40,41] and calcium signal abnormalities [42]. Shared genetic susceptibility has also been identified. Specific subtypes of epilepsy (childhood epilepsy with occipital seizures and benign childhood epilepsy with centrotemporal spikes) and migraine (familial hemiplegic migraine) have been linked to genetic mutations in *CACNA1A*, *ATP1A2* and *SCN1A* on chromosome 17 [41,43].

Attention-deficit hyperactivity disorder

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 [44]. Support for the comorbidity between epilepsy and attention-deficit hyperactivity disorder (ADHD) comes from national surveys [45], population-based study [46] and tertiary-care centers [47–49]. The influence of AEDs is often cited as a potential cause for the observed co-occurrence, 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 [47,48]. 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 co-occurrence include disruption of lipid metabolism, the norepinepherine system or the dopamine transporter system [46]. 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 [48]. 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 [50].

Limitations of epidemiologic research

Epidemiologic studies are characterized by several limitations that hinder the clear characterization of important features of epilepsy conditions and comorbid conditions. First, epidemiological studies rely primarily on self-report measures, which raises questions regarding their validity. Medical databases might provide a more accurate estimate of comorbid rates; however, very few studies in the epilepsy literature have used this approach and they are also suspect to drawbacks, such as incomplete recording and inconsistent definition of comorbidites. A second and related problem is that findings are often based on retrospective data and do not distinguish between current disorders and lifetime-to-date diagnoses. Third, information provided regarding the temporal contiguity of comorbidity (before or after onset of epilepsy) is limited. This is a critical issue for attempts to determine causality. Last, base rates of the comorbid condition in the general population are sometimes unknown or not presented. It would be helpful if these factors were taken into account in future surveys of comorbid conditions in epilepsy.

Conclusion

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, migraine and ADHD) are proving to have a complex connection whereby a shared underlying pathogenic mechanism may be responsible for the co-occurrence of epilepsy with these conditions. The same can be said for several other comorbid including Alzheimer's dementia, mental retardation and autism spectrum disorder [51,52]. Understanding the basis for the association of epilepsy and comorbid conditions poses important challenges for epilepsy diagnosis and management.

Future perspective

Increased attention to shared pathogenic mechanisms may reveal new mechanisms that link epilepsy and many of its comorbid conditions. Significant progress can be expected to be made in understanding the genetic and molecular basis linking epilepsy and its comorbid conditions. This could open up new possibilities for the development of therapeutics in managing epilepsy comorbidity.

Executive summary

Epilepsy & comorbidity

- Medical, psychiatric and cognitive comorbidities are common.
- Of individuals with epilepsy 26.8–84% have at least one medical comorbidity.
- Of individuals with epilepsy 5.9–64.1% have at least one psychiatric comorbidity.
- Cognitive comorbidity commonly occurs.

Causal models

- Epilepsy (or its treatment) causes comorbidity.
- Comorbid condition (or its treatment) leads to epilepsy.
- Shared underlying mechanism mediates the occurrence of epilepsy and comorbidity.

Bone health

- Bone health problems due to antiepileptic drug adverse effects.
- Compromised bone integrity and falls leads to higher rate of fractures.

Stroke

- Post-stroke epilepsy is the most common cause of epilepsy in the elderly.
- The risk of developing epilepsy after a stroke is increased by 23-fold.
- Cardiovascular abnormalities are common in those who develop epilepsy after stroke.

Depression

- Interictal depression is the most common psychiatric comorbidity.
- The presence of either depression or epilepsy puts one at an increased risk of developing the other.

- Antiepileptic drugs, biochemical factors, seizure-related factors and psychosocial variables contribute to high rates of both disorders.

Migraine

- Shares clinical features with epilepsy.
- Several comorbidities are common to both migraine and depression.
- Genetic link in specific types of epilepsy and migraine have been identified.

Attention-deficit hyperactivity disorder

- Attention-deficit hyperactivity disorder frequently predates seizure onset.
- Abnormalities in lipid metabolism, the norepinephrine system or dopamine transport are possible underlying factors.

Limits of epidemiological research

- Reliance on self-report measures.
- Retrospective research only.
- Little information regarding temporal contiguity of comorbidities.

Future perspective

- Increased attention on shared pathogenic mechanisms.
- A greater understanding of genetic and molecular basis should link to improved treatment and management.

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