Learning from the Comorbidities of Epilepsy

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Abstract:

Purpose of review: Comorbidities are a common feature in epilepsy, but neither the entire spectrum nor the significance of such comorbidities has been fully explored. We review comorbidities associated with epilepsy and their associated burden, provide an overview of relationships, and discuss a new conceptualization of the comorbidities.

Recent findings: The epidemiology of the comorbidities of epilepsy and effects on health outcomes, healthcare use, and healthcare expenditures have been partly delineated. Distinct mechanisms of the associations have been suggested but not entirely ascertained. Movement from conceptualizing epilepsy as a condition to a symptom-complex has occurred.

Summary: Comorbidities are common among people with epilepsy and are associated with poorer clinical outcomes and quality of life, greater use of health resources, and increased expenditure. Becoming aware of the associated mechanisms and their uncertainty is central to understanding the relationships between epilepsy and comorbid health conditions, which have implications for diagnosis and screening, medical management, and surgical management. Conceptualizing comorbidities of epilepsy as precipitating factors and epilepsy as the symptom will improve the understanding of epilepsy and catalyze research and improvements in clinical practice.

Keywords: antiepileptic drugs; antiseizure medications; outcomes; burden; seizures

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Introduction

Epilepsy is a common neurological disorder with a lifetime prevalence of 7 per 1,000 people and is associated with morbidity and premature mortality.[1] The prevalence of epilepsy is higher in low- and middle-income countries, among individuals with poor health, and in certain ethnicities.[1-4] Heterogeneity is the rule in epilepsy as it has differing semiologies, variable severity, a range of associated comorbidities and differing outcomes.[5] The natural history of epilepsy varies from spontaneous remission at one end of the spectrum to a chronic and debilitating condition at the other. Recently, as greater attention has been placed on developing nontraditional strategies to optimize outcomes and improve quality of life in people with epilepsy, the association between epilepsy and comorbidities has become prominent.[6, 7] Here, we define such comorbidities and their associated burden. We also provide an overview of their intertwined relationships and discuss a new conceptualization of comorbidities and epilepsy.[8]

The burden of Epilepsy Comorbidities

Epidemiology

Approximately 50% of adults and 80% of children with epilepsy have comorbid conditions.[9-12] They are up to eight times more likely than those without epilepsy to have neuropsychiatric conditions (depression, anxiety, bipolar disorder, attention deficit hyperactivity disorder, sleep disorders, dementias, movement disorders), and pain disorders (migraine, chronic pain, fibromyalgia, and neuropathic pain).[6, 13-15] The prevalence of asthma, autoimmune disorders, arthritis, heart disease, chronic lung disease, diabetes, and peptic ulcers is higher in people with epilepsy than in healthy controls.[6, 13-15] People with epilepsy are also more likely to have multiple comorbidities.[16] A recent study has validated this relationship among individuals younger than 50 years who experience sudden unexpected death in epilepsy (SUDEP).[17] Among children, 55% have additional medical disorders, 43% have developmental or psychiatric disorders, and 41% have other neurologic disorders.[10] More women than men with epilepsy have comorbidities;[18] the distribution of comorbidities differs between women and men, but psychiatric diagnoses are among the most common in both.[18] The comorbid disease burden may extend beyond formally recognized comorbidites. Approximately 11% of children without an established psychiatric diagnosis endorse suicidality.[19]

Health Outcomes

People with epilepsy experience poorer health outcomes than those without epilepsy. The risk of premature death is much higher amongst people with epilepsy than among those with migraine.[20] SUDEP and accidental death are often assumed to be the major causes of premature mortality, but this is more often due to comorbidities such as noncerebral neoplasms,

cardiovascular or cerebrovascular diseases.[21, 22] Comorbidities increase the risk of premature mortality among people with epilepsy, even among those seizure-free. [23, 24] Psychiatric comorbidities play an important role in premature mortality. People wit epilepsy who die from external causes, such as accidents and suicide, have higher depression and substance misuse odds than those without epilepsy or psychiatric comorbidity.[21] In addition to causing premature death, comorbidities complicate management, including causing poorer seizure control. Endocrine, psychiatric, and respiratory comorbidities are associated with lower probability of achieving remission when adjusted for demographic and clinical variables.[25] Psychiatric comorbidities predispose individuals to a lack of response to antiseizure medication (ASMs), perhaps through poor adherence, in addition to discharge against medical advice and non-attendance at appointments, contributing to premature mortality.[26-28] Contrary to previous assumptions, ASMs are not associated with an increased risk of suicide[29], although there is clear evidence that having epilepsy, particularly of temporal lobe origin, increases the risk of committing suicide.[30] Autism or cognitive disability predispose children to poorer long-term seizure outcomes.[31] Similarly, comorbidities are associated with poorer quality of life. Health-related quality of life is inversely related to comorbidities,[32] and depression and anxiety are associated with lower quality of life and higher risk of unemployment in adults.[33, 34] Intellectual disabilities, depression, and attention deficit hyperactivity disorder are associated with poor social adjustment and poor academic performance, irrespective of the severity and type of epilepsy.[35-37] Comorbidities and their effects seem independent of seizure activity.[38]

Healthcare Usage and Expenditures

People with epilepsy experience higher direct medical costs than those without epilepsy;[39] up to eighty per cent of direct medical costs in epilepsy are related to treating comorbidities rather than epilepsy.[40] They are also more frequent users of health services, as demonstrated by the increased risk of admission to hospital and more visits to physicians to address comorbid conditions.[41, 42] Similarly, people with epilepsy and comorbidities spend more on additional medications.[15] The presence of one comorbidity nearly triples the healthcare cost for epilepsy compared with those without a comorbidity,[18, 43] and overall healthcare costs increase with the number of comorbidities.[44] Depression is a notably costly comorbid condition, increasing total care costs by 83%.[43] The rise in healthcare costs per person associated with increased numbers of comorbidities is more significant for men than for women.[18]

Understanding Comorbidities

Mechanisms of Association

Given the current conceptualization of epilepsy, it is appropriate to consider the mechanisms of association between epilepsy and its comorbidities.[45-47] A classification scheme

delineated four mechanisms of association, including chance and artifactual comorbidities, causative mechanisms, resultant mechanisms, and shared risk factors[6]. There are also bidirectional effects.[6, 11] Chance comorbidities occur when the prevalence or incidence of a condition is equally common in a person with epilepsy as in those without, while artifactual comorbidity is an association that results from bias rather than from a true causal relationship.[6] Artifactual comorbidities may result from information bias, a systematic data collection error, leading to results not reflecting reality, or from selection bias, when the study population does not represent individuals with the condition of interest, leading to unrepresentative relationships between epilepsy and a given condition.[6, 48] Causative mechanisms occur when a comorbid condition leads directly or indirectly to epilepsy.[6] Resultant mechanisms occur when epilepsy leads to a comorbid condition due to the effects of seizures or treatments.[6] Shared risk factors are present when an apparent relationship results from a confounding factor that precipitates both epilepsy and comorbidity. This may be genetic, environmental, structural, or physiological.[6, 11, 49] Bidirectionally occur when two conditions are associated and extend beyond a reciprocal temporal sequence.[6]

There are three important caveats. First, the mechanisms above are not mutually exclusive in explaining the association of epilepsy with comorbidity, from the individual to the epidemiological level of the comorbidity.[6] Often, multiple mechanisms are active at any time. In the relationship between genetics, epilepsy, and comorbidities, a genetic factor may cause epilepsy, a shared risk factor, a cause of comorbidity, or a modifier of the causative or resultant association.[6] Similarly, multiple mechanisms within the same category may be active at once. Second, in different situations, some mechanisms of association may carry greater weight, reflective of the statistical concept of moderating variables.[50] Third, it is possible that other mechanisms have not yet been elucidated. Measurement of associations is foundational to explain the relationship between two conditions, but this is insufficient alone.

Role of Uncertainty

In some cases, the relationship between epilepsy and a comorbid condition is reasonably well-defined. For example, cerebrovascular diseases can cause epilepsy, mainly when cortical involvement, cerebral haemorrhage, or early seizures are present.[51] The exact mechanisms of association explaining the relationship between epilepsy and given comorbidity are often unknown. Uncertainty occurs in multiple areas. The precise mechanisms of association active for the individual or on an epidemiological level are unclear, as are their relative weights, the influence of potential mediating and moderating variables, and how these relationships change based on genetic and epigenetic alterations. The underlying biological pathomechanisms and the impact of other factors not yet identified or considered are also essential considerations. Previously, we have described three possible mechanisms for the comorbidity of epilepsy and type 2 diabetes mellitus (T2DM).[52] One mechanism suggested that mitochondrial dysfunction and adiponectin deficiency promote epilepsy, obesity, and T2DM, with the degree of each

pathogenic change determining the temporal development of each condition.[52] This is reflective of shared risk factors. Another mechanism suggested that people with epilepsy are more likely to be obese than those without epilepsy due to a lack of exercise and effects of certain ASMs, increasing susceptibility to T2DM through mitochondrial dysfunction;[52] this is a resultant mechanism. An additional mechanism could be that people with epilepsy have more significant mitochondrial dysfunction and lower adiponectin levels than those without epilepsy, exacerbated after treatment with ASMs.[52] The absolute or relative degree of mitochondrial dysfunction and adiponectin deficiency influences whether individuals develop T2DM, obesity, or both conditions;[52] this is another resultant mechanism. These potential mechanisms have not yet been validated in humans. As in this case, uncertainties permeate the relationship between epilepsy and other comorbid conditions.

Implications for Clinical Practice

The relationship between epilepsy and comorbidities has significant implications for clinical practice. The first domain of interest is screening and diagnosis. Early detection of comorbidities may lead to early intervention and health benefits.[6] The comorbidities of epilepsy may allow earlier detection of epilepsy by acting as an iatrotropic stimulus.[53] At present, the comorbidities of epilepsy are often under detected and undertreated, increasing morbidity and the risk of premature mortality.[54, 55] Screening instruments are available for conditions such as depression, alcoholism, and asthma in the general population, but similar screening instruments have not been developed for use in epilepsy [56-58] The validation of epilepsy-related screening tools would facilitate early intervention and improved individual outcomes. Similarly, an epilepsy diagnosis should increase suspicion for other disorders.[6] which, if detected, may guide stratification and phenotyping.[6] Comorbidities may also require treatment, in turn potentially improving seizure control.[6]

The second domain is treatment and medical management. The relationship between epilepsy and comorbid conditions may be affected in five ways within this domain. First, comorbidities and epilepsy may affect the choice of treatment for each other. Hepatic disease, renal insufficiency, migraine, or depression may affect the choice of ASM, while autoimmune diseases associated with seizures may be treated with immunotherapy.[6, 59] Second, determination of the medication regimen to treat comorbidities requires consideration of the effect of these on seizure susceptibility.[60] For example, some antipsychotics increase the risk of seizures.[61] Third, treating comorbidities may alter seizure control;[60] for example, antidepressants may reduce the risk of seizures.[62] Fourth, epilepsy treatment may improve or worsen the comorbidity.[63] Treatment with ASMs such as valproate, carbamazepine, and lamotrigine improves mood.[64] Fifth, pharmacokinetic interactions occur between ASMs and other medications;[60] this necessitates modifying the doses of both drug classes for optimal effect.[60] A recent study suggested an algorithm for selecting appropriate ASMs.[65] IASMs are stratified for provision to individuals by seizure types into three groups, with group 1 ASMs designated as preferred, group

2 defined as the second line, and group 3 defined as the third line.[65] The ranking of ASMs for the individual is adjusted based on clinical variables, including a variety of comorbidities.[65]

The third domain is epilepsy surgery. First, the comorbid disease burden may increase or decrease the feasibility of surgical management. An epilepsy-specific comorbidity index, rather than the Charlson comorbidity index, showed that a higher comorbid disease burden was strongly associated with reduced survival.[66] Second, epilepsy surgery can improve comorbidities, slowing or stopping the rate of cognitive decline in some epilepsies.[14] The outcome of surgery is associated with the degree of improvement in the comorbidity; seizure freedom and improved psychosocial status predict the remission of preoperative psychiatric conditions.[67] Third, comorbidities affect the degree of improvement following epilepsy surgery. Anxiety disorders and personality disorders may predict individuals at risk of remaining symptomatic or having low quality of life following epilepsy surgery, while autism or cognitive disability lead to worse seizure outcomes.[31, 68] Surgery and its associated technology have been identified as an essential source of information to improve the understanding of epilepsy and its comorbidities.[69] When considering medical or surgical management, a holistic approach focused on maximizing favourable outcomes while reducing the burden of comorbidities should be used.

A Way Forward

Some have previously considered epilepsy as a disease. There are two issues with this conceptualization. Misdiagnosis is relatively common in epilepsy.[70] Case ascertainment of epilepsy is challenging for multiple reasons[71, 72] and it is unclear whether all cases are identified due to the temporality of symptomatology and heterogeneity in presentation.[72] Second, there is no diagnostic gold standard for epilepsy,[72] and epilepsy definitions and classifications continue to change. The International League against Epilepsy has published a series of classifications, and newer classification schemes such as the four-dimensional classification and integrated epilepsy classification have been proposed.[73] It could also be said that epilepsy classifications are not pragmatic because they lack consideration of comorbidities, changes in the demography of epilepsy, brain development, genetic causes, and environmental triggers and do not harness the power of emerging technologies.[73, 74] Certain symptoms may be mistakenly attributed to epilepsy rather than comorbidities.[72] Lastly, there may be selection bias in assessed populations, and concealment may not be appropriately considered during investigational studies.[72]

In addition to challenges with case ascertainment, the epileptogenic process varies based on age, family history, and geographic variation.[7, 75] Many cases have a strong genetic basis.[7] A variety of single-gene disorders have been implicated in various types of epilepsy, as have common genetic mechanisms for the development of epilepsy.[73] Advances in genomic technology have only begun to delineate the genetic architecture of seizure disorders.[7] Similarly, multiple risk factors for epilepsy exist.[7] Congenital and developmental conditions are common in childhood, adolescence, and young adulthood, while cerebrovascular disease and cognitive disorders are common in the elderly.[7] Traumatic brain injury, central nervous system infections,

and tumours may occur at any age, though tumours are more likely in individuals over 40 years.[7] Endemic infections, including malaria and neurocysticercosis, are common risk factors for epilepsy in certain regions.[7] Triggers and epigenetic influences continue to be elucidated.[75]

The cause, demographics, presentation, treatment, and prognosis of epilepsy vary.[6] Epilepsy is, at its core, a tendency to have unprovoked seizures due to brain pathology or dysfunction. Thus it is more appropriately classified as a symptom complex.[72] Epilepsy is a spectrum of individual disorders which all cause epileptic seizures with associated biological, psychological, and social conditions, all of which rest on the foundation of comorbidities.[76, 77] Similarly, epilepsy is part of the functional spectrum of brain conditions involving abnormal paroxysmal neuronal or glial activity, including neurologic and psychiatric disorders.[6] A tendency toward paroxysmal activity is likely a shared risk factor for these conditions.[6] In light of these considerations, a new model conceptualizing the comorbidities of epilepsy as precipitating factors and epilepsy as the symptom is warranted. Employing this conceptualization in research and practice will streamline the classification of epilepsies, allow for improved management of people with epilepsy and promote innovation.

Conclusions

Comorbidities are common in epilepsy and result in poorer clinical outcomes and quality of life, greater use of health resources, and increased expenditure. Understanding the associated mechanisms and their uncertainty is central to elucidating the relationship between epilepsy and comorbid conditions, which has implications for diagnosis and screening and medical and surgical management. Conceptualizing comorbidities of epilepsy as precipitating factors and epilepsy as the symptom will improve the understanding of epilepsy and catalyze research and improvements in clinical practice.

Key Points:

- Comorbidities are common among people with epilepsy.
- Comorbidities have implications for diagnosis and screening, medical and surgical management.
- Epilepsy comorbidities affect health outcomes, healthcare use and expenditures.
- The entire spectrum and significance of epilepsy comorbidities are not fully understood.
- Conceptualize epilepsy comorbidities as precipitating factors and epilepsy as the symptom.

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