The comorbidities of epilepsy : concepts, challenges, and opportunities

Keezer, M.R.

CHAPTER 2
COMORBIDITIES OF EPILEPSY: CURRENT CONCEPTS AND FUTURE PERSPECTIVES

Mark R. Keezer[1,2], Sanjay M. Sisodiya[1,2], Josemir W. Sander[1,2,3]

[1] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

[2] Epilepsy Society, Chalfont St Peter, Buckinghamshire SL9 0RJ, UK

[3] Stichting Epilepsie Instellingen Nederland (SEIN), 2103 SW Heemstede, Netherlands

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ABSTRACT

The burden of comorbidity in people with epilepsy is high. Several diseases, including depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis are up to eight times more common in people with epilepsy than in the general population. Several mechanisms explain how epilepsy and comorbidities are associated, including shared risk factors and bidirectional relations. There is a pressing need for new and validated screening instruments and guidelines to help with the early detection and treatment of comorbid conditions. Preliminary evidence suggests that some conditions, such as depression and migraine, negatively affect seizure outcome and quality of life. Further investigation is needed to explore these relations and the effects of targeted interventions. Future advances in the investigation of the comorbidities of epilepsy will strengthen our understanding of epilepsy and could play an important part in stratification for genetic studies.

INTRODUCTION

Young adults have a median of two chronic health conditions, rising to six in people older than 65 years.[1] These findings have led some researchers to refer to the co-occurrence of several medical conditions in the same individual as a normal state of affairs.[2] A comorbid condition (or comorbidity) is one that occurs during the course of an index disease (eg, epilepsy). Comorbidities are generally defined in broad terms, including distinct clinical diseases and syndromes, and signs or symptoms of the index disease.[3]

Roughly 50% of adults with active epilepsy have at least one comorbid medical disorder.[2] Several large population-based studies report various conditions that are up to eight times more prevalent in people with epilepsy relative to the general population.[4, 5] Appreciation of the relevance of these comorbidities is increasing because they affect epilepsy prognosis and quality of life. For example, migraine and psychiatric comorbidities are associated with poor seizure outcome, whereas depression has been linked with reduced quality of life.[6, 7] Despite this growing appreciation, few data are available on the most effective methods to screen for comorbidities and the effect of interventions on prognosis.

Here, we describe ideas relevant to the investigation and conceptualisation of the comorbidities of epilepsy. We review the present state of knowledge of comorbidities associated with epilepsy and explore the ways in which research into comorbidities affords new opportunities for improvement in clinical care and scientific discovery.

MEASURING COMORBIDITY

A fundamental step in the study of the comorbidities of epilepsy is to understand the ways in which comorbidities are measured. An important measure of comorbidity burden is prevalence, which is generally understood to represent point prevalence—the proportion of individuals at risk with the condition in question at a single point in time.[8] When discussing the comorbidities of epilepsy, the emphasis is on whether the prevalence of comorbid conditions in those with epilepsy is different from that of the general population.[9] This assessment can be done by comparing prevalence estimates (eg, using 95% CIs or p values) or by reporting prevalence ratios. Additional factors, such as sex or age, could have a strong effect on the relative prevalence of two conditions. Adjusted prevalence ratios are an important method to control for such factors and can be calculated using straightforward statistical methods (appendix).[10, 11]

Whereas prevalence estimates are used to measure the burden of a single condition, comorbidity indices are useful instruments to measure the overall comorbidity burden of an individual. The Charlson[12] and the Elixhauser[13, 14] are the most commonly used indices, initially developed for use in observational studies to control for the potentially confounding effect of comorbidity burden on in-hospital mortality, length of hospital stay, and hospitalisation cost. These indices assign points to particular comorbid conditions when present, the sum of which is a weighted score designed to predict prognosis. The Charlson index assigns between 1 and 6 points for 19 different comorbid conditions, whereas the Elixhauser comorbidity measure assigns between −7 and 12 points for 21 conditions. These indices have been well validated in various populations,[15] but have only recently been validated in people with epilepsy.

An epilepsy-specific comorbidity index (ESI) was developed using a population-based administrative database of 7253 individuals with epilepsy in Calgary (AB, Canada).[16] The ESI includes 14 conditions (pulmonary circulation disorders, hypertension, cardiac arrhythmias, congestive heart failure, peripheral vascular disease, renal disease, solid tumour without metastases, paraplegia and hemiplegia, aspiration pneumonia, dementia, brain tumour, anoxic brain injury, moderate or severe liver disease, and metastatic cancer), each assigned 1–6 prognostic points. The total ESI score proved to be discriminating, with crude mortality ranging from 4.7 deaths per 1000 person-years for an ESI score of 0, to 535.6 deaths per 1000 person-years for a score greater than 10. The ESI has been validated and performed well in prospective longitudinal cohorts.[17]

MECHANISMS OF ASSOCIATION

Straightforward measurement of associations between different diseases has been referred to as an "empirical statistical phenomenon that has no meaning in itself".[18] Measurement of associations is only the first step in a process in which an additional goal is to understand why specific conditions are associated, which in turn might change our understanding of epilepsy and its clinical care.

Several models have been generated to account for the relation between comorbid disorders.[18-20] Such models are not mutually exclusive and the same comorbid condition could have many reasons for being associated with epilepsy, even in the same individual. Intellectual disability might occur in people with tuberous sclerosis, for example, as a result of the

underlying hamartomas or hamartia and as a result of the epileptic seizures (eg, in the context of West syndrome).[21, 22]

A classification scheme for the different mechanisms of association between epilepsy and comorbid conditions has been presented previously.[4] Here, we build on this initial scheme and incorporate additional aspects, dividing the mechanisms of association into five categories: chance and artifactual comorbidities, causative mechanisms, resultant mechanisms, shared risk factors, and bidirectional effects (figure 1).

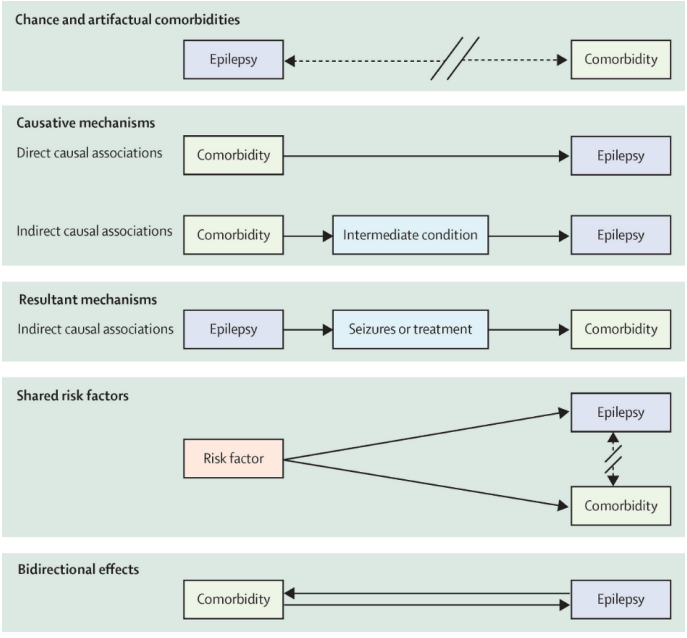

Figure 1: Mechanisms of association between epilepsy and its comorbidities. Each arrow with a solid line represents a casual association, with the cause leading to the effect. Arrows with dashed lines represent non-causal associations.

Chance and artifactual comorbidities

Chance refers to a circumstance in which the prevalence or incidence of a condition is as frequent in people with epilepsy as would be expected in the general population. Artifactual comorbidity is any non-causal association between epilepsy and a comorbid condition that arises

as a result of bias rather than a true causal relation. Artifactual comorbidity can be divided into two major forms: information bias and selection bias.

Information bias is defined as any systematic (ie, non-random) error in the data collected that leads to results that are different from the reality.[23] An apparent rise in the prevalence of a comorbid condition that is only as a result of inaccuracies in the identification of those with epilepsy or the comorbid condition is an example of information bias. Important subtypes of information bias are recall bias (eg, individuals with epilepsy are more likely to recall a past history of mild head trauma than those without epilepsy) and surveillance bias (eg, individuals with epilepsy are more likely to be closely monitored for other diseases).[24, 25]

Selection bias, the second form of artifactual comorbidity, occurs when the study population does not accurately represent those individuals initially eligible for inclusion in such a way that systematically alters the relation between conditions.[23, 26] Several types of selection bias are relevant to the investigation of the comorbidities of epilepsy. Referral bias can occur when participants are recruited from a specialised medical setting, in which only people with severe disease are studied, rather than the general population.[24] Non-response bias arises when particular factors affect some individuals' decisions to participate in a study.[26] Publication bias is a form of selection bias that is at the level of the overall study rather than the participants, which happens when specific data are not reported, as a result of bias on the part of authors, editors, or peer reviewers.[24, 26]

Causative mechanisms

Causative mechanisms are one of the simplest mechanisms of association. Here, the comorbid condition arises first, which then gives rise to epilepsy via direct or indirect causal mechanisms. Cerebrovascular disease, for example, directly causes about 10% of incident epilepsies,[27] whereas cigarette smoking can indirectly cause epilepsy as a result of neoplasm or stroke.

Resultant mechanisms

The resultant mechanism of association is similar to the causative model, but the temporal sequence is reversed— ie, epilepsy takes place first and subsequently gives rise to the comorbid condition. Aspiration pneumonia or seizure-related skeletal fractures are examples of resultant comorbidities of epilepsy. The resultant relation is probably an indirect association caused by the effects of seizures or the associated treatments, although this is yet to be proven.

Shared risk factors

Unlike the causative and resultant models, the shared risk factor mechanism of association is not indicative of a causal relation between epilepsy and its comorbidity. This model, in fact, describes a spurious (ie, biased) association as a result of a confounding factor, in which the confounder is defined as a common cause for epilepsy and the comorbid condition.[28] Unlike the other biased associations as seen in artifactual comorbidity, however, the causal relation between epilepsy, the comorbidity, and the shared risk factor is genuine (figure 1) and its investigation represents both a clinical imperative and a research opportunity. Shared risk factors can be genetic, environmental, structural, or physiological.[4] Perinatal hypoxaemic brain injury, for example, could result in epilepsy and comorbid spastic paraparesis.

Bidirectional effects

Bidirectional effects, also known as reciprocal effects, arise when two conditions can each cause the other.[8] Establishing that the temporal sequence is reciprocal (ie, that either could precede the other) is insufficient to prove bidirectionality. Variability in the temporal sequence of epilepsy and a comorbid condition could similarly occur in the context of the shared risk factor model. Some investigators have argued that there is a bidirectional relation between autism spectrum disorder (ASD) and epilepsy.[29] In the context of tuberous sclerosis, for example, this association is unlikely to be a bidirectional effect; but rather, in some individuals, the ASD might be identified before the onset of epilepsy and in others the reverse is true. This example is evidence of the potentially complex interaction between genetics, structural pathological changes, and environment, rather than evidence that ASD can cause epilepsy and vice versa. In other words, an important distinction exists between bidirectional causality and varying temporal sequence between individuals.

The role of genetics

The interplay between genetics, epilepsy, and its comorbidities is of interest and warrants particular attention. The various ways in which genetic factors relate to the comorbidities of epilepsy are summarised in figure 2. Perhaps most evident is the way in which genetic mutations might act as shared risk factors—eg, SCN1A mutations predispose individuals to the development of epilepsy and a gait disorder.[30] Such mutations are examples of genetic pleiotropy, in which the same genes can affect several different traits or disorders.[31]

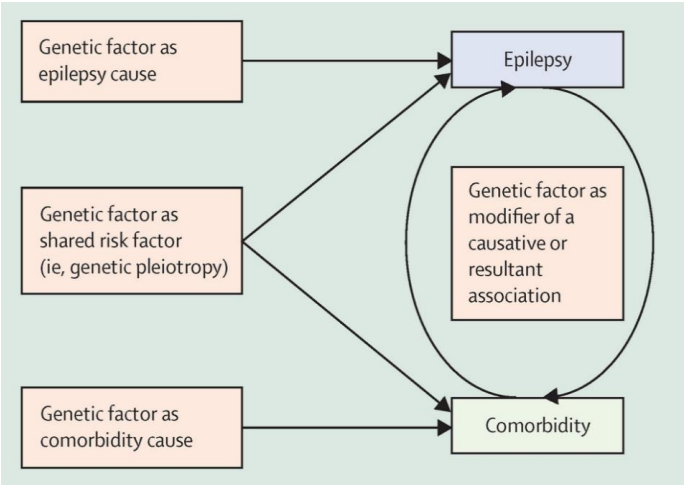

Figure 2: The relation between genetics, epilepsy, and its comorbidities

The interaction between genetics, epilepsy, and its comorbidities extends beyond genetic pleiotropy, however, and could include causative or resultant associations,[31] in which a genetic factor gives rise to condition A, which in turn causes condition B. A mutation of the TSC1 gene in tuberous sclerosis, for example, directly results in cortical tubers, some of which (along with surrounding cortical tissue) might result in epilepsy via a causative association.[32]

Genetic factors can also act as modifiers, acting as a third variable that affects the relation between a cause and effect—eg, epilepsy and a comorbidity.[33] Examples of such relations are the increased risk of epilepsy after traumatic brain injury in carriers of the APOE4 allele,[34] and the heightened risk of Stevens-Johnson syndrome after the initiation of carbamazepine in carriers of the HLAB*1502[35] or HLA-A*3101[36] alleles.

THE BURDEN OF COMORBIDITY

Several large and comprehensive studies have examined the comorbidity burden in people with epilepsy, and we now describe this research and the relevance of such comorbidities in the context of the concepts underpinning comorbidity research discussed above. These large studies have used population-based cohorts and administrative databases in the UK,[37] Canada,[38, 39] and the USA,[40-44] and have consistently shown a higher prevalence of several somatic and psychiatric conditions in people with epilepsy than in those without epilepsy (table).

Table: Relative prevalence of somatic and psychiatric comorbidities in people with versus without epilepsy, stratified by study[1]

	BRFSS (Kobau et al. 2008)[39]	CHIS 2005 (Elliott et al. 2009)[40]	CHS (Téllez-Zenteno et al. 2005)[35]	CHS (Téllez-Zenteno et al. 2007)[36]	EPIC (Ottman et al. 2011)[37]	GPRD (Gaitatzis et al. 2004)[34]	NHIS 2002 (Strine et al. 2005)[38]	NHIS 2010 (Kadima et al. 2013)[41]	NPHS (Téllez-Zenteno et al. 2005)[35]
	Telephone survey (U.S.A.)	Telephone survey (U.S.A.)	Door-to-door survey (Canada)	Door-to-door survey (Canada)	Postal survey (U.S.A.)	GP recorded diagnoses (UK)	Survey with face-to-face interviews (U.S.A.)	Survey with face-to-face interviews (U.S.A.)	Door-to-door survey (Canada)
Comorbidity (by ICD-10 chapter)	% in people with active epilepsy versus people without epilepsy (95% CI)	% in people with versus without epilepsy (95% CI)	PR (95% CI)	% in people with versus without epilepsy (95% CI)	PR (95% CI)	PR (95% CI)	Adjusted[2] POR (95% CI)	% in people with versus without epilepsy (95% CI)	PR (95% CI)
ICD chapter II: Neoplasm									
Neoplasm (unspecified)		11·1 (8·4, 14·4) vs 7·9 (7·6, 8·1)	1·4 (0·9, 2·1)				2·4 (1·7, 3·4)	11·3 (8·6, 14·9) vs 8·1 (7·7, 8·5)	1·2 (0·7, 2·1)
ICD chapter IV: endocrine, nutritional, and metabolic diseases									
Diabetes mellitus (unspecified)	13·0 (8·3, 19·7) vs 7·7 (7·4, 8·0)	7·7 (5·4, 10·9) vs 5·7 (5·4, 6·0)[3]	1·2 (0·9, 1·6)		1·0 (0·9, 1·1)	1·6 (1·4, 1·8)	1·3 (0·9, 1·9)	10·4 (7·7, 14·0) vs 8·7 (8·2, 9·1)	1·6 (1·2, 2·0)
Thyroid condition			1·6 (1·3, 2·1)						1·3 (0·9, 1·7)
ICD chapter V: Mental and behavioural disorders									
Major depression				17·4 (10·0, 24·9) vs 10·7 (10·2, 11·2)	1·3 (1·2, 1·4)	2·0 (1·9, 2·1)			
Anxiety				22·8 (14·8, 30·9) vs 11·2 (10·8, 11·7)	1·6 (1·5, 1·8)	2·0 (1·9, 2·1)			
ICD chapter VII: Eye and adnexa									
Glaucoma			1·2 (0·7, 1·9)						1·1 (0·6, 1·9)
Cataracts			1·2 (0·9, 1·6)						2·4 (1·9, 2·9)
ICD chapter VI: Nervous system									
Dementia (unspecified)						6·3 (5·5, 7·4)			4·3 (2·7, 7·4)
Alzheimer's disease						8·1 (5·9, 11·0)			
Migraine			2·0 (1·7, 2·3)		1·4 (1·3, 1·5)	1·6 (1·4, 1·8)	3·0 (2·3, 3·8)[4]	34·7 (30·1, 39·5) vs 16·2 (15·7, 16·8)[5]	2·6 (2·2, 3·0)
ICD chapter IX: Circulatory system									
Stroke (unspecified)	15·7 (11·3, 21·4) vs 2·4 (2·3, 2·6)	9·4 (6·9, 12·8) vs 2·2 (2·0, 2·4)	3·9 (2·7, 5·3)			7·0 (6·4, 7·6)	7·7 (5·1, 11·7)	14·3 (11·1, 18·2) vs 2·4 (2·2, 2·7)	4·7 (3·4, 6·2)
Heart disease (unspecified)	8·4 (5·6, 11·8) vs 4·6 (4·3, 4·8)	9·7 (7·3, 12·9) vs 6·2 (5·9, 6·5)	2·3 (1·9, 2·7)				2·5 (1·8, 3·4)	18·3 (14·7, 22·6) vs 11·3 (10·9, 11·8)	1·8 (1·4, 2·3)
Hypertension		28·8 (23·8, 34·3) vs 24·8 (24·2, 25·3)	1·1 (0·9, 1·3)		1·0 (0·9, 1·1)			34·2 (29·7, 39·0) vs 29·0 (28·4, 29·6)	1·9 (1·7, 2·2)
ICD chapter X: Respiratory system									

COPD		5·2 (3·6, 7·6) vs 1·9 (1·8, 2·1)	2·9 (2·0, 4·0)						1·9 (1·3, 2·5)
Chronic bronchitis						1·7 (1·3, 2·2)		7·5 (5·2, 10·6) vs 4·1 (3·8, 4·5)	
Emphysema						1·3 (0·7, 2·3)		5·5 (3·5, 8·3) vs 1·7 (1·5, 2·0)	
Asthma	20·3 (15·3, 26·4) vs 8·2 (7·8, 8·6)	21·9 (18·2, 26·2) vs 12·6 (12·1, 13·1)	1·4 (1·1, 1·7)		1·3 (1·1, 1·4)	1·3 (1·2, 1·4)	1·8 (1·4, 2·4)	19·2 (15·2, 24·0) vs 12·6 (12·0, 13·2)	1·1 (0·8, 1·3)
ICD chapter XI: Digestive system									
Peptic ulcers			2·5 (2·0, 3·2)			1·9 (1·6, 2·4)		12·4 (9·2, 16·5) vs 6·2 (5·8, 6·6)	2·7 (2·1, 3·4)
Bowel disorders (Crohn's/Ulcerative colitis)			2·0 (1·4, 2·7)						3·3 (2·4, 4·3)
ICD chapter XIII: Musculoskeletal system and connective tissues									
Allergies			1·2 (1·0, 1·3)						1·6 (1·4, 1·8)
Back problems			1·4 (1·2, 1·6)						1·5 (1·3, 1·7)
Fibromyalgia			1·5 (0·9, 2·4)		2·0 (1·7, 2·3)				
Arthritis (unspecified)	43·0 (37·0, 49·2) vs 28·0 (27·5, 28·6)	32·3 (27·4, 37·5) vs 18·9 (18·5, 19·3)	1·4 (1·2, 1·6)				2·3 (1·7, 3·0)[6]	30·9 (27·3, 34·8) vs 21·4 (20·8, 22·0)	1·5 (1·3, 1·7)
ICD chapter XIV: Genitourinary system									
Urinary incontinence			3·2 (2·4, 4·1)						4·4 (3·5, 5·5)

BFSS, Behavioral Risk Factor Surveillance System; CHIS, California Health Interview Survey; CHS, Community Health Survey; EPIC, Epilepsy Comorbidities and Health Survey; GPRD, General Practice Research Database; NHIS, National Health Interview Survey; NPHS, National Population Health Survey; GP, general practitioners; PR, prevalence ratio; OR, prevalence odds ratio; TIA, transient ischemic attack; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; GO, gastrointestinal.

[1] Lifetime prevalences are reported, unless otherwise indicated.

[2] Adjusted for age, sex, race/ethnicity, education, marital, and employment status.

[3] Limited to type 2 diabetes mellitus.

[4] Defined as a history of severe headache or migraine over the last three months.

[5] Includes a history of severe headaches.

[6] Includes osteoarthritis, rheumatoid arthritis, gout, lupus, and fibromyalgia.

Many of the associations between epilepsy and the listed comorbid conditions are not surprising in view of their known roles as causes of epilepsy (eg, CNS neoplasm, stroke, and Alzheimer's disease).[45] Arrhythmias might occur as a result of the effect of antiepileptic drugs.[38] Shared risk factors could account for the relation between epilepsy and heart disease (ie, shared vascular risk factors that lead to stroke) or migraine (ie, excessive cortical hyperexcitability).[42, 46] The association between epilepsy and diabetes seems to be especially true for type 1 diabetes and might be related to the shared presence of anti-glutamic acid decarboxylase (GAD) antibodies, which are strongly associated with type 1 diabetes (in about 80% of individuals) and are present in up to 6% of people with epilepsy.[47] Allergies have been suggested to be the effect of specific antiepileptic drugs in some people, and asthma might occur as a result of associated environmental and living conditions that might be indirectly related to epilepsy.[4] The burden of comorbidities in people with epilepsy is higher, but their distribution seems to be similar to that in the general population, with more prevalent migraine, asthma, and brain neoplasms in individuals younger than 64 years and more prevalent cerebrovascular and cardiovascular disease, and meningioma in individuals older than 64 years.[37]

Many studies have consistently reported an increased burden of several comorbidities in people with epilepsy. The degree to which these associations between epilepsy and comorbid conditions result from artifactual comorbidity rather than true causal relations is uncertain. Many of the studies discussed above relied on unvalidated screening instruments to identify individuals with or without epilepsy and with or without comorbidities.[37-39, 41, 43, 44] Of note, evidence suggests that if individuals with epilepsy are asked whether or not they have epilepsy, around a quarter of the group will say that they do not,[48] which emphasises the importance of an accurate screening instrument. For conditions such as migraine or fibromyalgia, which are frequently underdiagnosed[49, 50] (especially in the case of mild disease), a higher prevalence in people with epilepsy than in those without epilepsy in these observational and retrospective studies could conceivably be as a result, at least in part, of recall or surveillance bias. The response rate was approximately 50–60% in several studies,[40, 42, 44] rising as high as 75–85% in others.[38, 39, 41] Not surprisingly, investigations that relied on telephone or postal surveys had lower response rates, placing them at particular risk of non-response bias. To maximise accuracy, future studies should be population-based to produce findings that are more generalisable and at lower risk of referral bias, use prospective data collection to reduce the risk of recall bias, use only validated screening

and diagnostic methods to minimise the risk of misclassification bias while also applying these equally to all participants to minimise surveillance bias, ensure a high response rate to minimise non-response bias, and ensure that all results are reported to minimise the risk of publication bias.

All of the aforementioned studies are cross-sectional (ie, a single snapshot in time) and conclusions regarding whether the comorbid condition or epilepsy arose first are speculative. Some longitudinal studies have been conducted and reported bidirectional effects between epilepsy and several conditions, including depression,[51, 52]suicidality,[51, 52] anxiety,[51] psychosis or schizophrenia,[53, 54] autism,[29] migraine,[55] stroke,[56, 57] and dementia.[58, 59] Whether these associations are truly bidirectional or as a result of variable temporal sequence, however, is unclear. Future studies, preferably experimental studies that can ascertain the causal nature of such associations and the direction of the relation, are needed.

RELEVANCE AND IMPLICATIONS

Screening and diagnosis

One of the more fundamental features of the comorbidities of epilepsy is their effects on the time of detection of the index disease since they might act as an iatrotropic stimulus.[3] Regular neurological follow-up in individuals with a known brain neoplasm, for example, will enable earlier detection of a seizure disorder.

Understanding which comorbidities might develop in people with epilepsy is equally relevant. A report by the US Institute of Medicine emphasised the importance of the early identification of comorbid conditions in people with epilepsy.[29] The idea is that early detection would lead to early intervention and tangible health-care benefits for the patient. Psychiatric, cognitive, and several somatic comorbidities (eg, migraine and osteoporosis) are frequently undetected and undertreated in people with epilepsy.[60-63] The Institute of Medicine recommended that relevant organisations "establish and disseminate a standard screening protocol for people with epilepsy that implements screening on a regular basis for comorbidities…".[29] Screening instruments and guidelines exist for conditions such as osteoporosis and depression in the general population; however, these methods have not been translated and validated for use in people with epilepsy.[29] The absence of such instruments and guidelines is a clear and pressing gap in epilepsy care.

Treatment, prognosis, and quality of life

The presence of comorbid conditions can affect therapeutic decisions in people with epilepsy. Comorbid hepatic disease or renal insufficiency, migraine, or depression, for example, could be relevant in decisions about antiepileptic drugs, while the risk of cognitive deficits might preclude some surgical options—eg, risk of severe memory impairment from temporal lobectomy.

Investigation of the potential relation between autoimmune disease and epilepsy is expanding. One study reported a statistically significantly elevated prevalence of epilepsy in 135 394 individuals with autoimmune disease (ie, type 1 diabetes, psoriasis, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, myasthenia gravis, and coeliac disease).[64] This association has potentially important implications for epilepsy treatment in some cases, because, for example, individuals with epilepsy and anti-GAD antibodies can be successfully treated with immunotherapies.[64]

Increasing evidence shows that treating comorbidities might also affect the degree of seizure control. An analysis of the US Food and Drug Administration data on psychotropic drugs, extracted from phase 2 and 3 clinical trials with 75 873 participants, showed that those given antidepressants were less likely to have an incident epileptic seizure.[65] Similarly, treatment of the seizures could affect the comorbidity. The rate of cognitive decline seen with some epilepsies, for example, could be slowed down or even reversed by epilepsy surgery.[66]

Comorbid conditions might allow for so-called prognostic anticipation,[3] in which their presence could affect, and therefore allow some prediction of, the prognosis of the index disease. Comorbidity has been associated with increased risk of mortality, functional status, quality of life, and different aspects of health care in the context of several index diseases.[67] For instance, migraine was associated with a reduced probability of early antiepileptic drug response and seizure freedom.[8] Psychiatric disease was associated with a higher risk of pharmaco-resistance[68] and worsened outcome after anterior temporal lobectomy.[69]

Comorbid health conditions in children with new-onset epilepsy have been associated with reduced quality of life.[70] Intellectual disabilities and conditions such as depression and attention deficit hyperactivity disorder have been independently associated with poor social adjustment and academic underachievement in children with epilepsy, independent of the

severity and type of epilepsy.[71-74] Similar comorbid conditions in adults, including depression and anxiety, have been associated with reduced quality of life and a higher risk of unemployment.[7, 75]

Health-care cost and use

The health-care costs associated with the co-occurrence of medical conditions in the general population are substantial. An investigation that examined direct healthcare-related costs in a random sample of 1 217 103 Medicare beneficiaries (aged 65 years or older) in the USA reported that individuals with at least two chronic conditions (defined according to their expected persistence or recurrence)[76] represented 65% of beneficiaries and accounted for 95% of Medicare expenditures.[77] An examination of American private insurance claims data showed that in people with epilepsy 80% of direct medical costs were not related to epilepsy, but were related to the treatment of comorbid somatic and psychiatric conditions.[78] People with epilepsy who have a high comorbidity burden are at increased risk of admission to hospital and generally incur medical costs almost 1.4 times higher than do individuals without such comorbidities.[79] A study of 824 483 American veterans, aged older than 66 years, showed that veterans with new-onset epilepsy were at significantly greater risk of medical admission over a 4-year period than were veterans without epilepsy (odds ratio 4 .84, 95% CI 4 .29–5 .46). The five most important predictors of medical admission were heart attack (4 .74, 2 .72–8 .28), gallbladder disease (3 .90, 1 .21–12 .58), anaemia (2 .93, 2 .09–4 .10), angina (2 .57, 1 .57–4 .22), and alcohol dependence (2 .46, 1 .49–4 .08).[80]

Mortality

Premature mortality in people with epilepsy is increasingly a focus of research.[81, 82] The role of epilepsy-related causes of death in premature mortality is often emphasised,[83] but the role of comorbidities should not be overlooked. A meta-analysis of unexpected death in epilepsy showed that only 4% of deaths in low-risk groups of people with epilepsy in high-income countries were attributable to sudden unexplained death in epilepsy,[84] which is generally regarded as the most common, single cause of epilepsy-related death.[85]

Almost all deaths in people with epilepsy are related to the comorbidities of epilepsy—particularly neoplasm, cardiovascular, or cerebrovascular disease.[86, 87] Around three-quarters of deaths within one year of epilepsy onset are directly related to the underlying epilepsy cause in individuals with symptomatic epilepsy, rather than seizure-related causes.[88] Data from the

National General Practice Study of Epilepsy, a community-based UK study with almost 25 years of follow-up, has shown that people with epilepsy are more likely than the general population to die of malignant neoplasms, ischaemic heart disease, cerebrovascular disease, and pneumonia, after controlling for the effects of age, sex, and calendar year.[89] The heightened risk of death from neoplasms persisted even after excluding cerebral neoplasms, and was postulated to be caused by the purported pro-neoplastic effect of some antiepileptic drugs or an underlying shared genetic predisposition.[89] A report from Sweden showed that individuals with epilepsy and a history of depression or substance abuse were at increased risk of death from external causes, including suicide and accidental death.[90]

FUTURE DIRECTIONS

Two major ways in which the investigation of comorbidities offers opportunities to further our understanding of epilepsy relate to the evolving notion of epilepsy as a spectrum, or part of a spectrum, and to their use as an important instrument in the study of genetics.

We have generally referred to epilepsy as a single, implicitly uniform entity, but epilepsy is, in fact, highly heterogeneous in terms of its cause, demographics, clinical manifestations, treatment, and prognosis. It is best understood as a collection of individual disorders that share an abnormal tendency to cause epileptic seizures, consisting of dozens of epilepsy syndromes.[91]

Indeed, epilepsy can be rationally defined as a disorder characterised not only by epileptic seizures, but also by its associated biological, psychological, and social conditions.[92, 93] The comorbidities of epilepsy form the core of these associated conditions and contribute to our evolving conceptualisation of epilepsy as a spectrum.[94, 95]

Epilepsy can also be regarded as part of a functional spectrum of brain conditions characterised by abnormal paroxysmal neuronal or glial activity. This predisposition towards paroxysmal activity could be deemed a shared risk factor. Some such comorbidities are in the neurological realm, such as migraine, but others, such as depression, fall within psychiatry. The concept of the phenotype of epileptic seizures will not disappear, but an evolving appreciation of the functional range of neurological disease will have a major effect on clinical interpretation, diagnosis, and treatment.

In terms of the genetics of epilepsy, phenotyping is an important technique in the investigation of gene function and the identification of harmful mutations. The process of

phenotyping relies on identifying relevant comorbidities in specific groups of individuals. Syndromic epilepsies, with conspicuous congenital comorbidity profiles, lend themselves to genetic investigation; DOORS syndrome, for example, is characterised by a combination of sensorineural deafness, onychodystrophy, osteodystrophy, and intellectual disability with seizures.[96] One investigation, however, showed that even in individuals with sporadic epilepsy initially thought to be nonsyndromic, genetic factors could account for both the epilepsy and comorbid somatic or psychiatric conditions, some of which might not be evident unless carefully considered or sought.[97] Irrespective of the potential difficulties, all comorbidities, including even the most inconspicuous, should be regarded as part of the stratification and phenotyping in cases of epilepsy.

CONCLUSIONS

The comorbidities of epilepsy represent a substantial burden for people with epilepsy. The clinical and scientific community should continue to move forward, not only to focus on the description of the statistical relation between different conditions, but also to deconstruct the causal mechanisms for these comorbidities, while bearing in mind the risk of artifactual comorbidity. Screening instruments and guidelines should be developed to help translate the knowledge we have acquired into effective and meaningful clinical interventions. Existing evidence shows that the potential benefit of such endeavours is great. The study of the comorbidities of epilepsy has the potential to transform our understanding of epilepsy, as research into these comorbid conditions helps to clarify the concept of epilepsy as part of a functional spectrum and the important role of genetics.

CONTRIBUTORS

All authors contributed to the original concept of the manuscript. MRK drafted the manuscript and all authors revised the manuscript.

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APPENDIX

Incidence (generally referring to cumulative incidence) and prevalence (generally referring to point prevalence) are mathematically related but are especially distinguished by study context. Incidence is a measure of the number of newly affected individuals, in a population at risk of the outcome of interest, over a specified time interval (ie, a longitudinal study).[1] The incidence of seizure recurrence, for example, following anterior temporal lobectomy is 44% over 12 months.[2] Prevalence, on the other hand, is a measure of the number of affected individuals, in a population at risk, at a given point in time (ie, a cross-sectional study).[3] The prevalence of migraine, for example, is 27.9%.[4] Note that incidence is a measure of disease "risk" while prevalence is a measure of disease "burden".

Prevalence ratio (PR) is the ratio of the prevalence of a disease in one population over the prevalence of the same disease in a second population. A PR greater than 1.0 denotes a relative increase, while a PR less than 1.0 denotes a relative decrease, in prevalence in the first population relative to the second.

Additional factors, such as age or sex, may have a strong influence on the relative prevalence of a condition in two different populations. Adjusted PRs are an important method to control for such factors and may be calculated using log-binomial regression or Poisson regression with robust standard errors.[5,6] It is preferable to avoid reporting odds ratios (the

natural output of logistic regression) given that they overestimate the associated PR (in the context of a cross-sectional study; risk ratio in the context of a longitudinal study), especially when the outcome of interest is common.[7-9]

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