Epilepsy as a systemic condition: link with somatic co-morbidities

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Abstract word count: 247

Manuscript word count: 2990

Manuscript includes 3 tables, 1 figure, and 2 supplementary materials.

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Abstract

Background: People with epilepsy have more concomitant medical conditions than the general population; these co-morbidities play an important role in premature mortality. We sought to generate explanatory hypotheses about the co-occurrence of somatic co-morbidities and epilepsy, avoiding causal and treatment-resultant biases.

Methods: We collected clinical, demographic and somatic co-morbidity data for 2016 consecutive adults with epilepsy undergoing assessment at a tertiary centre and in 1278 people with epilepsy in the community. Underlying causes of epilepsy were not classed as co-morbidities.

Results: Somatic co-morbidities were more frequent in the referral centre (49%) where people more frequently had active epilepsy than in the community (36%). Consistent risk factors for co-morbidities were found in both cohorts. Using multivariable ordinal regression adjusted for age, longer epilepsy duration and an underlying brain lesion were independently associated with a smaller burden of somatic conditions. The treatment burden, measured by the number of drugs to which people were exposed, was not an independent predictor. Shorter epilepsy duration was a predictor for conditions that conceivably harbour significant mortality risks.

Conclusions: Somatic co-morbidities do not occur randomly in relation to epilepsy; having more severe epilepsy seems to be a risk factor. Independently from age, the early period after epilepsy onset appears to be at particular risk, although it is not clear if this relates to an early mortality or to a later decrease of the burden of co-morbidities. These results suggest that, for some people, epilepsy should be considered a systemic condition not limited to the CNS.

Introduction

Several large community studies using either self-reported diagnoses or registers have shown a higher prevalence and incidence of somatic conditions in people with epilepsy than in the general population(1-8). Co-morbidities, defined classically as "any additional distinct clinical entity"(9) from epilepsy, were found to be increased globally, affecting the majority of conditions assessed in each study. There is evidence that this increased prevalence is not fully explained by over-representation of unfavourable socio-economic factors among people with epilepsy(10) or reporting bias caused by greater contact with medical services(8). Several lines of evidence also confirm that, when excluding epilepsy-related health issues, people with epilepsy have a worse health status than people in the general population. People with epilepsy have a greater utilisation of healthcare services for co-morbid conditions(11), incur higher healthcare costs than the general population after excluding epilepsy-related costs(12), and have increased premature mortality seemingly unrelated to epilepsy(13).

Most epidemiological studies analysing prevalence of co-morbidities are confounded by causal (some co-morbidities may be the cause of epilepsy) and resultant (co-morbidities may be the consequence of epilepsy or its treatment) associations(14), lacking data on the temporal course of the conditions. These biases do not seem, however, to explain the increased burden of co-morbidities; people with epilepsy were shown to be more likely to die prematurely due to cerebrovascular disease, even those without a stroke before epilepsy onset(15) and regardless of treatment exposure(7).

Very little is known about the mechanism(s) underlying the increased burden of somatic co-morbidities in epilepsy. Migraine with aura, for instance, was shown to have a bidirectional association (migraine with aura increasing the risk of developing epilepsy and vice-versa)(16, 17), suggesting common underlying risk factors(18). Better understanding of the mechanisms of co-morbidities could help to prevent morbidity and premature mortality in people with epilepsy.

We assessed the prevalence and predictors of co-morbid conditions in widely different settings, accounting for the whole spectrum of epilepsy, to generate explanatory hypotheses for the increased burden of somatic co-morbidities in epilepsy. In contrast to previous studies on co-morbidities, availability of medical assessment allowed us to minimise biases due to causes, results and treatment of epilepsy, so identifying genuine co-morbidities.

Methods

We recorded all current and previous medical and psychiatric diagnoses distinct from epilepsy in two different adult populations with epilepsy: people seen at a referral centre and people in the

community. People seen at the referral centre were included as part of an audit of all people with chronic epilepsy admitted to our assessment unit at Chalfont St Peter, UK, over ten years between 2001 and 2011. People with epilepsy in the community consisted of two groups. The first included people enrolled in the National General Practice Study of Epilepsy and Epileptic Seizures (NGPSE) study[19], a nation-wide prospective study of people with epilepsy followed by general practitioners; we included people with definite and probable epilepsy (according to whether episodes were considered as definite or probable epileptic seizures), up to their last available assessment. The second group constituted an audit at 10 general practices in the Chilterns region (west of London) in 2001 and 2002; people were identified through records of antiepileptic drug (AED) prescription; the diagnosis of epilepsy was then confirmed through medical records review by a specialist epilepsy nurse. At the referral centre, co-morbidities are systemically recorded as part of the admission process. Somatic and psychiatric co-morbidity diagnoses relied on diagnoses documented by general practitioners or self-reported by the individual; psychiatric co-morbidities were reassessed if needed at the referral centre. At the referral centre, somatic conditions were not specifically re-evaluated except if part of the investigation of epilepsy. Demographic data and epilepsy characteristics were recorded in both cohorts. Family history of epilepsy and seizure types were also documented in the tertiary centre cohort based on descriptions and, when available, on observation and recording. Family history was considered as positive when more than one member of the family (genetically related) has/had seizures. Location of the seizure onset zone in the cohort assessed at the referral centre was documented, defined where possible through a combination of seizure semiology and EEG recordings. All antiepileptic medications to which the person had been exposed were recorded in both populations; AEDs were also classified according to whether they significantly induce liver enzymes (phenobarbital, phenytoin, carbamazepine) or not[20]. The total dose of AEDs to which each person had been exposed was not available; we used the number of AEDs over the duration of the epilepsy censored at assessment as a surrogate. Traumatic brain lesions that were presumed not to be the cause of the individual's epilepsy, and conditions that were clearly the direct exclusive consequence of traumatic lesions, were not considered as co-morbidities. Indirect consequences of traumatic lesions (for instance venous thrombosis after a fracture) would be considered as co-morbid. A decision was made to exclude hay fever, appendicectomy, tonsillectomy, hysterectomy (without a clear diagnosis, or for premenopausal menorrhagia), and unspecified skin conditions (without further details) from the analyses. Those conditions or the conditions leading to those procedures were likely to have been reported inconsistently. All phenomena considered by the treating consultant to be the direct effect of treatments (such as hyponatremia in people taking carbamazepine or kidney stones in those on topiramate) were not considered, in order to exclude as far as possible resultant co-morbidities.

Conditions considered at the assessment to be the causes of epilepsy (genetic or structural) were recorded separately to exclude causal co-morbidities. People assessed at the referral centre systematically underwent MRI scanning, whereas people in the community had had MRI or CT scans or neither. Risk factors for the cause (such cerebrovascular risk factors in stroke) were not considered as part of the cause. A structural abnormality was presumed to be the cause of epilepsy when the localisation of the seizure onset zone (based on semiology and electrophysiological recording) was in keeping with the localisation of the lesion at imaging. Brain injuries (such as meningitis), even if leading to minimal structural changes, were considered as structural causes if they occurred before seizure onset. As discussed above, traumatic brain injury was considered as causal only if there was a temporal association and localisation of epilepsy concordant with the known injury. . For cortical development malformation, an underlying cause (such a genetic condition reported as causal) was not considered as co-morbidity but as part of the cause. Haemorrhagic complications of a vascular malformation were not considered as a co-morbidities. Degenerative conditions or inflammatory conditions (such as multiple sclerosis) were considered as a causal only if there was no alternative explanation and the disease preceded epilepsy onset. Conditions (for example, genetic conditions) where epilepsy is commonly encountered were considered as co-morbidity only if seizure semiology and the seizure onset zone were exclusively in keeping with another clear focal structural cause of epilepsy. Intellectual disabilities were recorded separately and not considered as co-morbidities as seizures and causes of epilepsy can account for their occurrence(21). Focal neuropsychometric deficits in keeping with the epilepsy focus were also not considered co-morbidities. Genetic conditions were considered to be the cause of epilepsy if seizures are widely regarded as a part of the genetic syndrome in the OMIM database (http://www.omim.org/) or through a literature review (PubMed). Other clear features of a genetic syndrome (angiomyolipoma in tuberous sclerosis, for example) were not considered as co-morbid conditions, but as part of the underlying genetic syndrome. Genetic generalised epilepsy (idiopathic generalised epilepsy) was not considered as a genetic causation of epilepsy as genetic mechanisms are likely to be complex and definitive genetic causes have been demonstrated only in a minority of cases(22).

As in previous studies that considered the whole unselected burden of somatic conditions(4, 11), co-morbidities were grouped into categories (e.g. circulatory, genitourinary, nervous system) according to the WHO International Classification of Diseases and Related Health Problems 10th Revision (ICD 10) chapters (http://apps.who.int/classifications/icd10/browse/2010/en). Potential predictors with small numbers (<15) per outcome category (predictors such as idiopathic epilepsy, genetic cause) in the community cohort were not included in the multivariable analyses (supplementary material 2).

Chi squared and Mann-Whitney tests were used for univariable analysis of predictors of the numbers of co-morbidity categories. Multivariable stepwise backward ordinal logistic regression was used to analyse the factors influencing the number of systems (none, one, or two or more) affected by co-morbidities. P values of <0.05 were considered statistically significant overall and variables with univariable p value <0.1 were included in multivariable regression. Assumptions (proportionality of odds ratios, co-linearity) were checked.

We sought to adjust for age and found an interaction between age and co-morbidities in the community cohort and so the analysis was stratified with a division at 60 years. There was no interaction in the referral centre cohort (the cohort was younger on average), so a simple regression adjustment for age was used (implemented as $[age-mean\ age]^2$).

Multivariable logistic regression was then used to assess the effect of each identified predictor on specific co-morbidity categories (yes/no) adjusting for factors found significant in the previous analyses. For the analysis of predictors of specific co-morbidity categories, we performed a Bonferroni correction for multiple testing. Statistical analyses were performed with SPSS (v20; SPSS inc) and Stata (v13; Statacorp Inc.).

The study was approved by the institutional Ethics Committee.

Results

We collected data from general practices for 1278 people diagnosed with epilepsy, and from the referral centre for 2016 people with chronic epilepsy assessed there. Demographic and clinical data for both cohorts are presented in Table 1. At the time of assessment, all people at the referral centre had active epilepsy, while 87% of the community cohort had not experienced seizures for at least one year. Those at the referral centre had been exposed to a greater number of AEDs than those in the community. Among people at the referral centre, 37% (750) had temporal lobe epilepsy, 17% (352) frontal epilepsy, 16% (323) multifocal or generalised epilepsy, 0.8% (16) occipital epilepsy and 0.7% (15) parietal epilepsy; the seizure onset zone could not be determined.

All conditions considered as co-morbid can be found in supplementary material 1. People at the referral centre significantly more often had somatic co-morbidities (49%) than people in the community (36%; Table 1). Somatic co-morbidities were significantly more frequent than psychiatric ones in both cohorts (36 vs 11% in the community and 49 vs 23% in the referral centre cohort). When correcting for age and gender, people from the referral centre were at significantly increased risk to

have somatic co-morbidities (OR: 2.6, 95% CI: 2.2-3.1, p<0.0001). Functional systems affected by co-morbid conditions (co-morbidity categories) are shown in Figure 1.

Predictors of the burden of comorbidity

Factors associated with the overall burden of co-morbidities are detailed in Table 2 for each cohort. Multivariable analyses in both cohorts showed that longer epilepsy duration and presence of an underlying brain lesion were independently associated with a reduced burden of somatic co-morbidities, independently of age (Table 2). In the referral centre, female gender was a significant risk factor for a greater burden. The presence of psychiatric co-morbidities was not a significant predictor of the burden of somatic co-morbidities for either cohort, neither was localisation of the seizure onset zone in the referral centre cohort, nor seizures in the year preceding the assessment in the community cohort. The number of AEDs to which individuals were exposed was not a significant predictor of the number co-morbidity categories, but the total number of AEDs or of enzyme-inducing AEDs to which people had ever been exposed were significantly correlated with epilepsy duration in both cohorts.

Predictors of specific comorbidity categories are detailed in Table 3.

Discussion

Our study shows that every second person with epilepsy seen at a referral centre and every third in the community has at least one somatic co-morbid condition, disregarding causes of epilepsy and direct consequences of its treatment. In the only previous study considering all co-morbidities(4), the prevalence of all co-morbidities was increased 1.5 fold in people with epilepsy, which is similar to our results compared with general population studies using similar methodology(23, 24). Co-morbidities can indeed be classified as causing epilepsy, resulting from epilepsy or its treatment, and those with no obvious association. Including indiscriminately all concomitant condition would not satisfied the original definition of co-morbidities proposed by Feinstein ("distinct additional clinical entity" (9)) as causal or resultant conditions are intimately linked with the disease. Studying co-morbidity apparently not linked with epilepsy, may allow us, however, to explore if epilepsy has wider implication than commonly thought, that may explain the treatment and cause independent premature mortality found in this condition (13). We intended to draw out mechanistic hypotheses from the epidemiological relationship between epilepsy and co-morbidities, as finding predictors of the burden of somatic co-morbidities would provide insight into the co-occurrence of epilepsy and other somatic conditions. This was impossible in previous studies (1-8) given the limited data available on the conditions reported and epilepsy in the registries or questionnaires.

The two populations we assessed to explore the spectrum of epilepsy differed widely, in terms of the proportion of people in remission and the number of AEDs to which people were exposed. The prevalence of somatic co-morbidities was significantly higher in the cohort of people seen at the referral centre, despite their younger age. The prevalence of co-morbidities was not, however, assessed in exactly the same way in both cohorts (people in the community were followed in general practice in the long term without any formal reassessment, while those at the referral centre were actively reassessed), but we aimed to reduce bias by discarding conditions potentially not reported consistently. A greater prevalence of ECG abnormalities(25), of obesity(26) and a higher mortality rate due to cancer(27) have been already reported in people with drug-resistant epilepsy: greater exposure to antiepileptic medication has been hypothesised as the explanation. In our study, the influence of AEDs was assessed as a global effect, and did not account for the role of specific AEDs in particular conditions (such as polycystic ovary syndrome). Treatment burden was correlated with epilepsy duration and was not an independent predictor. This is in line with a life-long follow-up study(28) where the major determinant of premature mortality due to co-morbidities was seizure frequency in people that had similar treatment exposure. We hypothesise that the difference between the two cohorts suggest that greater seizure frequency, rather than treatment exposure, could be the major determinant of the association of co-morbidities with greater epilepsy severity.

Many common chronic conditions, such as inflammatory conditions(29), asthma(30), diabetes and obesity(31) are associated with significantly increased burdens of cardiovascular conditions and cancers compared with the general population. Disease severity in those conditions also seems to be a predictor of the occurrence of co-morbidities(32), which are widely considered as the consequence of low grade chronic systemic inflammation(33, 34). It is increasingly clear that epilepsy, mostly probably as a consequence of seizures, induces a systemic inflammatory response in the long term(35). Several clinical studies showed that there is a plasma peak of pro-inflammatory interleukin 6 after seizures (35-40) lasting up to 72 hours (41). Those changes were also found interictally in people with chronic epilepsy (35, 42). Other pro-inflammatory changes, such as increased interleukin 1β (IL-1β) or tumour necrosis factor α (TNF-α) or decreased interleukin 1 receptor antagonist (IL-1ra) have been shown less consistently (36-39). A recent study (43) found significantly higher levels of interleukin 17 (IL-17), interferon γ (IFNγ), IL-1β, interleukin 6 (IL-6) in people with epilepsy than in healthy controls. Recently C-reactive protein (CRP) was also shown to be increased post-ictally in people with epilepsy in comparison with healthy controls (44). These cytokines are associated with the development of a wide range of somatic conditions. Increased serum IL-6 levels were shown to be an independent cardiovascular risk factor (45, 46). In healthy people, increased IL-6 was shown independently to predict the occurrence of other cardiovascular risk factors of myocardial infarction

(47) and diabetes type 2 (48). In people with previous myocardial infarction, it independently predicts the occurrence of congestive heart failure (49) and cardiovascular deaths (50). Increased CRP level was found to predict the occurrence of several cancer types (ovarian (51, 52), colorectal (53), or lung cancer (54)), independently from other risk factors such as smoking. One hypothesis would be that repeated peaks of systemic inflammation induced by seizures, leading to long term low grade systemic inflammation, could contribute to the increased occurrence of somatic co-morbidities. There are indeed recent suggestions that life expectancy in people with epilepsy is partially correlated with inflammatory markers (55).

Shorter epilepsy duration, independently from age, was a rather counterintuitive predictor of a greater burden of somatic co-morbidity categories such circulatory conditions, suggesting that the early period after epilepsy onset is one of particular risk, which is in line with a previous study(6). Early referral because of associated co-morbidities seems unlikely, as the same effect was seen in the community cohort where people were routinely followed. A possible hypothesis would be that people with a greater burden of co-morbidities early in the course of epilepsy may die prematurely and thus not be seen later. This is also in keeping with a study(28) showing increased premature mortality due to co-morbidities early in the course of the disease in people with the greatest seizure frequency.

In the referral centre cohort, being female was a predictor of a higher burden of somatic conditions, affecting endocrine/metabolic/nutritional and musculoskeletal conditions. This probably relates to females being at risk of osteoporosis(56) or of gender-specific conditions such as polycystic ovary syndrome(57) in combination with the increase probability of exposure to AEDs such as valproate in the large number of drugs tried (our model did not take into account specific conditions combined with exposure to specific medication).

The presence of an underlying lesion (structural epilepsy) was found to protect against a spectrum of somatic co-morbidities in both cohorts. People without a clear cause may have been more thoroughly assessed at the referral centre and more concurrent diagnoses may have been reported in discharge summaries to maximise reimbursement, but this seems unlikely as co-morbidities were systemically recorded during admission before investigation results were known. A study in people with epilepsy without an identified structural cause found significantly larger chromosomal deletions, encompassing significantly more genes, than in a group of healthy controls group(58). It could be hypothesised that people with non-structural epilepsy (a measure limited by varying imaging qualities in our study) might have a stronger genetic contribution to the epilepsy, making them potentially more liable to harbour more somatic conditions.

Somatic co-morbidities are commonly overlooked, possibly because of their heterogeneity, the presumed influence of AEDs, or because somatic co-morbidities are not felt to be related to epilepsy. Our results, suggesting a consistent link between seemingly unrelated somatic conditions and epilepsy (although they do not demonstrate it), are further evidence that epilepsy has wide physiological implications even in people with apparently mild epilepsy. Seizures, or their treatment, cannot fully explain the burden of somatic conditions, as people with mostly controlled epilepsy were also shown to have a significant premature mortality due to co-morbidities(13), independently from AED treatment(7). Effects of epileptic syndromes (especially epilepsy without structural abnormalities or "cryptogenic" epilepsy) should therefore be considered as not limited to the central nervous system, and the overall health of people with epilepsy (including those with controlled seizures) should be carefully evaluated. General health of people with epilepsy should not be considered as unrelated to the disease and should also be a concern for the treating specialist.

Our study has several limitations. People in the community did not undergo a comprehensive assessment and, for example, the prevalence of idiopathic generalised epilepsy (genetic generalised epilepsy) and underlying structural lesions were probably underestimated, overemphasising the proportion of people with epilepsy of unknown origin in the community. The assessment of co-morbid conditions is also limited by the use of medical records; we did not directly assess somatic co-morbidities using diagnostic tests. The retrospective design may bias the results through the varying degree of attention paid by the caring physicians. The cohorts were also not fully contemporary and both sets of data were collected over a decade; secular lifestyle changes may have been confounders over that period, although the predictors found seem unlikely to have been influenced by environmental factors over that time period. Finally, the low pseudo R^2 of the multivariable analyses suggest that our model predicted only a small part of the variation of the burden of somatic co-morbidities; socio-economic factors, ethnicity, lifestyle, and educational level (which were not available systematically in records) would probably also have explained part of the variation(10). Ageing is obvious also a major determinants of the burden of co-morbidities, our analyses showed however that the associations described were age independent.

Conclusions

Somatic co-morbidities are very common in people with epilepsy and do not occur randomly in relation to the epilepsy. Epilepsy severity is a risk factor. The increased burden of somatic co-morbidities in people without a clear underlying brain lesion could suggest a genetic predisposition for the co-occurrence of epilepsy and somatic co-morbidities. Independently from age, the early period after epilepsy onset appears to be at particular risk, possibly because co-morbid conditions

lead to premature mortality. Epilepsy should be considered as a systemic condition not limited to the CNS. <mark>Other somatic conditions should not be considered as completely unrelated to the disease and should also be a concern for the treating specialist.</mark>

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