Epilepsy & Behavior 78 (2018) 57–61

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Epilepsy is a neurological and a systemic disorder

Alan W.C. Yuen [a,b,*], Mark R. Keezer [a,b,c,d], Josemir W. Sander [a,b,c]

[a] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, WC1N 3BG London, UK
[b] Chalfont Centre for Epilepsy, Chalfont St. Peter SL9 0RJ, UK
[c] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, The Netherlands
[d] Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec H2L 4M1, Canada

ARTICLE INFO

Article history:
Received 19 September 2017
Accepted 7 October 2017
Available online xxxx

Keywords:
Comorbidities
Mortality
Inflammation
Oxidative stress
Glycation
Methylation

ABSTRACT

The basic pathophysiology of epilepsy is still not fully understood. Epidemiological evidence for epilepsy seems to suggest that it may not only be the propensity for seizures to occur. The high prevalence of comorbidity and the finding that premature mortality is still increased in those who are in long-term remission, suggest that there is a systemic component to the condition. This systemic component is an additional shared risk factor that can explain an important proportion of the comorbidities of epilepsy as well as how an individual with inactive epilepsy remains at an elevated risk of premature mortality. This systemic component can be viewed from the perspective of a number of fundamental pathophysiological processes: inflammation, oxidative stress, glycation, and methylation capacity. These processes are associated with all-cause mortality and there is also a growing understanding of their impact on seizure processes. We propose that epilepsy be considered as the sum of seizures and comorbidities caused by systemic dysfunction, and that the comprehensive management of epilepsy should also include the management of the systemic dysfunction.

1. Introduction

Despite recent progress, the basic pathophysiology of ictogenesis and epileptogenesis is still not fully understood [1–3]. In parallel, a number of observations suggest that epilepsy may not be just a neurological condition — it is not just the propensity to have unprovoked seizures. It appears to be more complex, and there is a growing appreciation that it is important to understand fully all the factors that are at play in people with epilepsy to allow the clinician to manage the individual better. We examine observations that suggest that epilepsy is not just a neurological condition and that there is also a systemic component. We propose a schema for the basic elements affecting the propensity for seizures to occur. What we propose, is a significant shift in the way we consider epilepsy and, clearly, in the next steps, these concepts require further investigation and verification.

2. Epilepsy is not just a neurological condition

2.1. High prevalence of comorbidity

Studies have consistently shown that numerous psychiatric and somatic conditions are more prevalent in people with epilepsy than in those without. These comorbid associations have been summarized recently [4]. The most important associations include structural and functional diseases of the central nervous system such as stroke, dementia, and migraine, but nonneurological disorders are also increased. For instance, heart disease, hypertension, chronic obstructive pulmonary disease, and neoplasm are more likely to occur in people with epilepsy than in the general population [4]. A cross-sectional analysis of Canadian data derived from almost 180,000 people surveyed between 1998 and 2001 showed that the prevalence of digestive tract ulcers was at least 2.5 times greater in individuals with epilepsy than in those without [5]. In the same study, gastrointestinal disorders (i.e., Crohn's disease and colitis) were 2.0 to 3.3 times more prevalent [5]. In an UK study of 1,041,643 individuals surveyed between 1995 and 1998, dementia was 5 to 25 times more likely (depending on age) in people with epilepsy while gastrointestinal hemorrhage was overall 2.6 to 4 times as likely as well, along with congenital cardiac abnormalities which were almost 9 times more likely [6].

Psychiatric comorbidities are common among people with epilepsy. The most frequent are depression, anxiety, and psychosis, but schizophrenia has also been reported [4]. In the UK, depression and anxiety have been reported to be almost twice as common in people with epilepsy [6]. Similar findings have also been seen in Canada and the USA [7,8]. A recent systematic review reported that 6% of individuals with epilepsy suffer from comorbid psychosis [9].

2.2. Premature mortality is still increased in those who are seizure-free

Multiple studies have shown an increased risk of premature death in people with epilepsy as compared with the general population. This has

* Corresponding author at: Chalfont Centre for Epilepsy, Chalfont St. Peter SL9 0RJ, UK.
E-mail addresses: alan@yuen.co.uk (A.W.C. Yuen), mark.keezer@umontreal.ca (M.R. Keezer), l.sander@ucl.ac.uk (J.W. Sander).

https://doi.org/10.1016/j.yebeh.2017.10.010
1525-5050/

been summarized in a recent systematic review prepared by the Mortality Task Force of the International League Against Epilepsy [10]. Sudden unexpected death in epilepsy and status epilepticus are important causes of epilepsy-related death but these generally account for fewer than 5% of deaths [11]. The majority of underlying causes of death are related to somatic comorbidities. The most frequent of these are noncerebral neoplasm, cardiovascular disease, and cerebrovascular disease [11]. Those with more severe epilepsy, convulsive rather than nonconvulsive seizures, are at greater risk of death [10]. Interestingly, however, among those who are seizure-free, the risk of premature mortality remains elevated. In a cohort of 695 individuals with a history of epileptic seizures, even among those with only a single notified seizure, the risk of an early death compared with the general population after almost 25 years of follow-up was increased by between 49% (in those with an unknown cause) and 72% (in those with a putative etiology), controlling for differences in age, sex, and calendar year [12].

2.3. Evidence of systemic dysfunction

The increased prevalence of many comorbid conditions in people with epilepsy as well as the persistent risk of increased premature mortality, seems to suggest that there is a nonneurological component to epilepsy. There are multiple means by which comorbidities may be related to epilepsy [4]. Among these, the shared risk factor model explains an important proportion of the comorbidities of epilepsy as well as how an individual with inactive epilepsy remains at an elevated risk of premature mortality. Shared risk factors may be genetic (e.g., a SCN1a mutation resulting in epilepsy and cardiac arrhythmia) or structural (e.g., traumatic brain injury resulting in epilepsy and cognitive deficits). We propose that systemic dysfunction is an additional shared risk factor that may explain these observed relationships.

2.4. Proposed 'new' delineation of epilepsy

We propose that epilepsy is the sum of the seizures and comorbidities (see Fig. 1). Seizures are the result of the epileptogenicity of the epileptic focus/abnormal neuronal networks. The epileptic focus has an inherent propensity to produce seizures but this propensity can be aggravated by systemic dysfunction and reduced by antiepileptic drugs. As well as its effects on epileptogenicity, the systemic dysfunction is also the basis for the comorbidities.

3. The nonneurological components of seizure disorder

Human physiology is complex and not fully understood, particularly, how most ill health develops. Our prevailing medical model seeks specific causes for specific illnesses, but there is a growing appreciation that there may be fundamental pathological processes underlying most illnesses. Hence, some diseases may have the same underlying pathophysiological processes, and individuals manifest different illnesses due to genetic and constitutional differences. From this perspective, the development of ill health or systemic dysfunction can be viewed from several different fundamental processes including genetic [13] and epigenetic causes [14]; mitochondrial efficiency [15,16]; pathophysiological biochemical processes and psychological stress. These processes are not fully distinct and there is substantial overlap between them. Currently, our knowledge base does not allow us to view the development of ill health from the perspective of one overarching process. We will look at ill health from the perspective of a growing understanding of a few fundamental pathophysiological biochemical processes which appear to underlie ill health. We will also look briefly at mitochondrial efficiency as the fundamental underlying process.

4. Pathophysiological biochemical processes as the basis for systemic dysfunction

Several pathophysiological biochemical processes that appear to be the basis for systemic dysfunction have been identified. There are biomarkers for these processes and multiple large scale epidemiological studies have shown that they are associated with all-cause mortality, suggesting that these pathophysiological processes are essential and can lead to ill health and mortality from all the major causes. The impact of these processes on ictogenesis and epileptogenesis is less well-defined but there is now a growing understanding of how they can have an impact on epilepsy.

4.1. Chronic systemic inflammation

Chronic systemic inflammation is the result of the release of proinflammatory cytokines from immune-related cells and the chronic activation of the innate immune system. It is a physiological state which differs from acute inflammation where there are clinical symptoms and signs. Serum C-reactive protein (CRP) is a commonly used biomarker for systemic inflammation. There is clear evidence from many observational studies suggesting that CRP levels are associated with cardiovascular and all-cause mortality. In a cohort study with 231,000 person-years of follow-up (median 14.3 years), CRP was positively associated with risk of all-cause, cardiovascular and noncancer noncardiovascular mortality independent of established risk factors. The hazard ratio of all-cause mortality (95% confidence interval (CI)) for those with CRP in the >10 mg/l (versus <0.5 mg/l) was 1.87 (1.43–2.43) in men and 1.98 (1.50–2.63) in women [17]. In a study involving over 70,000 subjects, cross-sectional analysis showed that higher levels of CRP were associated with higher risk of psychological distress and depression. The prospective analyses showed increasing CRP levels were also associated with increasing risk for hospitalization with depression [18].

Systemic inflammation is thought to have an influence on the epileptogenic process. Any brain injury, such as trauma, stroke, viral infection, febrile seizures, and status epilepticus, occurring at any time in life is a risk factor for developing epilepsy. After these events, brain inflammation develops [19] suggesting that a proinflammatory state in the brain might play a role in epileptogenesis [20]. This hypothesis is supported by two main lines of evidence: (1) the upregulation of

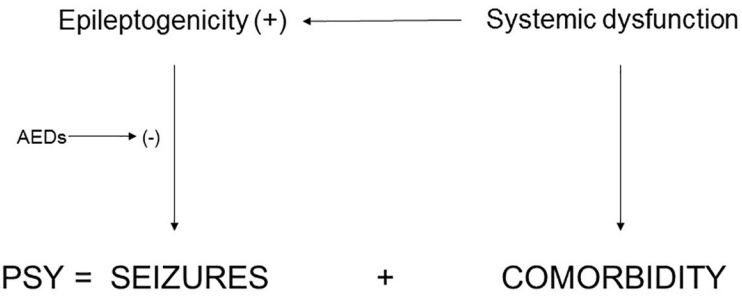

Fig. 1. Schema to show the role of systemic dysfunction in producing comorbidities and increasing epileptogenicity to produce seizures. Legend: arrows = leads to/influences; (+) = increasing; (−) = decreasing; AEDs = antiepileptic drugs.