



Neurological Disorders: Epilepsy

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Article info

Received: 10/02/2024

Revised: 22/02/2024

Accepted: 21/03/2024

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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.

Key words: Comorbidities, Mortality, Inflammation, Oxidative stress, Glycation, Methylation

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.

Epilepsy is not just a Neurological condition 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].

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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].

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 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].

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.

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.

The Non Neurological 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.

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 welldefined but there is now a growing understanding of how they can have an impact on epilepsy

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 N10 mg/l (versus b0.5 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 proinflammatory signals during epileptogenesis in the epileptic foci; and (2) pharmacological targeting of specific proinflammatory pathways after status epilepticus or in kindling shows antiepileptogenic effects. The proinflammatory molecules' effect on increasing hyperexcitability probably involves rapid, nontranscriptional effects on glutamate and gamma-aminobutyric acid (GABA) receptors, and transcriptional activation of genes involved in synaptic plasticity [20]. The glia, especially the astrocytes and microglia, are thought to be intimately involved in the inflammatory processes contributing to epileptogenesis [21]

Oxidative stress

Reactive oxygen species (ROS), including superoxide radical, hydrogen peroxide, hydroxyl radical, and singlet oxygen, are generated during normal cellular metabolism [22,23]. Physiological levels of ROS can be scavenged by enzymatic (e.g., superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and peroxiredoxins) and nonenzymatic (e.g., vitamin C, vitamin E, and reduced form of glutathione) antioxidant defense systems. Excessive ROS levels, however, due to increased ROS production, decreased antioxidant defense ability lead to oxidative stress [24]. Excess ROS further reacts with nitric oxide (NO) generating reactive nitrogen species such as peroxynitrite [25,26]. Several studies undertaken in different clinical settings have shown an association between increasing oxidative stress and mortality risk. As an example, a study of 21,031 participants followed for a median of 5.8 years showed that

those with a greater balance of antioxidant to prooxidant lifestyle exposures had significantly lower all-cause, cancer and noncancer mortality [27]. The brain is particularly susceptible to oxidative stress as it uses higher amounts of oxygen than other organs. The brain also contains high concentrations of polyunsaturated fatty acids that are prone to lipid peroxidation, is rich in iron, which can catalyze hydroxyl radical formation, and is low in catalase activity. Oxidative stress results in functional cellular disruption and cellular damage and may cause subsequent cell death. Protein oxidation leads to functional changes or deactivation of various enzymes [28]. Lipid peroxidation causes membrane structure alterations that affect membrane fluidity and permeability and membrane some neurological conditions and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [30,31]. Oxidative stress is one of the possible mechanisms in the pathogenesis of epilepsy, or it may be one of the contributing mechanisms. Oxidative stress is thought to disrupt intracellular calcium homeostasis gradually, leading to increased neuronal excitability, seizure susceptibility, and vulnerability to additional stress and neuronal cell loss. Mitochondrial dysfunction is intimately linked to oxidative stress, and they are thought to be important in acute injuries and the development of acquired chronic epilepsy [32,33].

Glycation

Glycation is the nonenzymatic covalent bonding of reducing sugars, such as fructose or glucose, to proteins, lipids, or nucleic acids, leading to the formation of advanced glycation end-products (AGEs). This reaction is known as Maillard's or browning reaction. Glycation is part of normal metabolism, but excessive accumulation of AGEs in the tissues and in the circulation leads to pathogenic effects. Glycation is accelerated by hyperglycemia, hence, is a particular problem for people with diabetes. The production of AGEs can result in cross-linking of body proteins, leading to alteration of tissue structure and function. Pathogenic effects are also mediated by AGEs' ability to increase inflammation and oxidative stress [34]. Advanced glycation end-products are generated in the body and also ingested as part of our diet. Dietary AGEs (dAGEs) are mainly

produced by especially dry heat and high temperature cooking [35]. Glycation, through the generation of AGEs, is thought to be a causal factor in a whole gamut of human illnesses. Indeed, many large scale epidemiological studies have demonstrated an association between Hemoglobin A1c (HbA1c), a marker of glycation, and all-cause mortality both in Western populations [36–38] and in a Japanese population [39]. There has been very little research on AGEs and epileptogenesis [40], but there is very good evidence that AGEs increases systemic inflammation and oxidative stress [41], and thus have an impact on seizures through these mechanisms.

Methylation capacity

Methylation is the biochemical process of transferring a methyl ($-CH_3$) group to organic molecules in the human body. Methylation is critical to nucleic acid synthesis, deoxyribonucleic acid (DNA) methylation (one of the main mechanisms for epigenetic changes), synthesizing neurotransmitters, homocysteine metabolism, protein methylation, and liver detoxification. Methylation capacity can be assessed by measuring a number of different molecules, and measuring homocysteine is one such measure. Inadequate methylation capacity as indicated by raised homocysteine is seen in different diseases, including congenital birth defects, late pregnancy complications, neurodegenerative and psychiatric diseases, osteoporosis, and cancer [42]. In a study including 1933 elderly subjects from the original Framingham Study cohort, followed for a median of 10 years, the unadjusted relative risk for all-cause mortality was 2.18 (95% CI, 1.86–2.56) for the upper quartile of nonfasting total plasma homocysteine levels vs the lower 3 quartiles. The study showed that elevated plasma total homocysteine levels are independently associated with increased risk of all-cause mortality in the elderly [43]. Studies have also shown associations between higher homocysteine levels and the incidence of stroke. One study has shown that the observed increase in risk of stroke among individuals homozygous for the methylenetetrahydrofolate reductase (MTHFR) T allele is close to that predicted from the differences in homocysteine concentration conferred by this variant. This was suggested to

be consistent with a causal relation between homocysteine concentration and stroke [44]. Plasma homocysteine levels are elevated in several neurological conditions including epilepsy [45]. Homocysteine appears to potentiate seizures and cell loss in animal models of epilepsy [46]. Homocysteine may contribute to ictogenesis through a variety of mechanisms including its ability to inhibit GABA [47].

Mitochondrial Efficiency as the basis of Systemic Dysfunction

Mitochondrial dysfunction has been implicated in the aging process and various human disorders, such as cardiovascular and neurodegenerative diseases, cancer, migraine, infertility, kidney and liver diseases, and toxicity of drugs [48–50]. It is recognized that the physiological role of mitochondria widely exceeds that of solely being the biochemical power plant of our cells [48]. Mitochondrial efficiency is particularly important for neurological functions as the brain constitutes 2% of the body mass yet accounts for 20% of the body's total oxygen consumption. Recently, epilepsy has been reported in people who have mitochondrial respiratory chain dysfunction, even when most of them do not have a specific phenotype as previously described (e.g., myoclonic epilepsy in myoclonic epilepsy with ragged-red fibers (MERRF)) nor due to specific gene mutation or deletions [51,52]. In a study of human brain specimens from 57 people with temporal lobe epilepsy and two control subjects, specific deficiency of complex 1 of the mitochondrial respiratory chain was demonstrated in the hippocampal CA3 region in those with hippocampal foci and in the parahippocampus in those with parahippocampal foci. This suggests that mitochondrial dysfunction at the epileptic focus may be a mechanism contributing to the altered neuronal excitability [53].

Implications

The evidence that epilepsy is associated with increased comorbidity is now irrefutable. Together with the observation that even people with epilepsy in remission have an increased risk of early mortality, this suggests that there is a systemic component contributing to their ill health. These observations lead us to suggest that it may be helpful to consider epilepsy to be the sum of seizures and comorbidities and that there is

a systemic dysfunction that is the primary contributor to the comorbidities. This systemic dysfunction can also aggravate epileptogenicity and increase seizure occurrence. The basis of this systemic dysfunction can be considered from the perspective of the pathophysiological processes discussed above. We have provided the evidence as to how these processes are associated with ill health and how they can modify epileptogenicity. What might be the implication of accepting this view of epilepsy? If it is accepted that systemic dysfunction can aggravate epileptogenicity and is the main contributor to the comorbidities, then the comprehensive management of epilepsy should be focused not only on stopping seizures, but strategies to ameliorate the systemic dysfunction – reducing systemic inflammation, glycation, oxidative stress, and increasing methylation capacity – are needed.

Acknowledgments

We are grateful to Dr. Gail S. Bell for her critical review of the manuscript. This work was carried out at UCLH/UCL Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. JWS receives support from the Dr. Marvin Weil Epilepsy Research Fund, and the UK Epilepsy Society endows his current position. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Cite this article as:

Kumar B., Zulphilar A., Tiwari H. and Chandrul K. K. (2024). Neurological Disorders: Epilepsy. *Int. J. of Pharm. & Life Sci.*, 15(3): 15-24.

Source of Support: Nil

Conflict of Interest: Not declared

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