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Epilepsy Is Associated With Increased Long-Term Risk of Cardiac Arrhythmias: Did Your Heart Skip a Beat?

Epilepsy and Long-Term Risk of Arrhythmias

Wang J, Huang P, Yu Q, Lu J, Liu P, Yang Y, Feng Z, Cai J, Yang G, Yuan H, Tang H, Lu Y. Eur Heart J. 2023;44(35):3374-3382. doi:10.1093/eurheartj/ehad523. PMID: 37602368; PMCID: PMC10499547

Background and aims: Previous evidence has mainly supported transient changes in cardiac function during interictal or peri-ictal phases in people with epilepsy, but the long-term risk of cardiac arrhythmias is poorly described. This study aimed to assess the long-term association of epilepsy with cardiac arrhythmias, considering the potential role of genetic predisposition and antiseizure medications (ASMs) in any associations observed. Methods: This population-based study evaluated UK Biobank data for individuals recruited between 2006 and 2010. Cox proportional hazards models and competing risk models were used to examine the association of epilepsy history with the long-term incidence risk of cardiac arrhythmias and arrhythmias subtypes. Polygenic risk scores (PRS) were calculated to investigate the effect of genetic susceptibility. The role of ASMs was also evaluated by integrating observational and drug target Mendelian randomization (MR) evidence. Results: The study included 329 432 individuals, including 2699 people with epilepsy. Compared with those without epilepsy, people with epilepsy experienced an increased risk of all cardiac arrhythmias [hazard ratio (HR) 1.36, 95% confidence interval (CI) 1.21-1.53], atrial fibrillation (HR 1.26, 95% CI 1.08-1.46), and other cardiac arrhythmias (HR 1.56, 95% CI 1.34-1.81). The associations were not modified by genetic predisposition as indicated by PRS. Competing and sensitivity analyses corroborated these results. Individuals with epilepsy using ASMs, especially carbamazepine and valproic acid, were at a higher risk for cardiac arrhythmias. This observation was further supported by drug target MR results (PSMR $<$ .05 and PHEIDI $>$ .05). Conclusion: This study revealed the higher risk of cardiac arrhythmias persists long term in people with epilepsy, especially among those using carbamazepine and valproic acid. These findings highlight the need for regular heart rhythm monitoring and management in people with epilepsy in order to reduce the risk of further cardiovascular complications.

Commentary

The interaction between the heart and the brain has been a topic of intellectual discourse since antiquity through the contested cardiocentric versus encephalocentric source of our emotions. In the world of epilepsy, it continues to attract a great deal of attention due to the arrhythmological complications encountered in the peri-ictal phase and the potential link to sudden unexpected death in epilepsy.[1] It is widely accepted that seizures may cause arrhythmias through autonomic dysregulation and, conversely, cardiac arrhythmias may induce seizures through cerebral hypoxia.[2] Yet, the association of epilepsy with the long-term risk of cardiac arrhythmias through cellular and structural remodeling has been less extensively studied and constitutes the topic of the current study.[3]

Specifically, Wang et al[3] dissected the records of 329 432 individuals, including 2699 patients with documented epilepsy, recruited between 2006 and 2010 in the UK Biobank database. Participants with a priori heart disease or a posteriori epilepsy were excluded from the analysis. Several demographic, medical, and lifestyle parameters were collected, including genetic susceptibility risk scores and use of anti-seizure medications (ASMs). After a mean follow-up of 12.5 years, the association of epilepsy history with the long-term incidence risk of cardiac arrhythmias was calculated using various Cox proportional hazards regression models that adjusted for potential confounders. People with epilepsy (PWE) experienced an increased risk of all cardiac arrhythmias (hazard ratio [HR] 1.36, 95% confidence intervals [CI] 1.21-1.53) and their subtypes that was not modified by genetic predisposition. Compared to people without epilepsy, PWE but without ASMs had an increased risk of cardiac arrhythmias (HR 1.28, 95% CI 1.04-1.58), while those with both epilepsy and ASMs had an even higher risk (HR 1.40, 95% CI 1.22-1.60), especially if they were exposed to carbamazepine and valproic acid.[3]

This population-based study[3] drew from a large cohort of PWE and controls over a long period of time. It collected extensive

information on genetic profiles, acquired comorbidities and medical treatments that are potentially involved in the generation of cardiac arrhythmias. Through several statistical subanalyses, it controlled for potential confounders, in an attempt to elucidate the risk for cardiac arrhythmias attributed solely to epilepsy itself versus the role of ASMs.

On the other hand, inescapable drawbacks commonly seen in large epidemiological studies were present in this one as well.[3] Despite efforts to minimize the misclassification bias of self-reporting, the documentation of epilepsy was not based on electrographic confirmation and expert adjudication, particularly if nearly one third of PWE were not on ASMs. As already acknowledged by the investigators, crucial information regarding the type, frequency, and location of the seizures, as well as the disease duration and severity were missing. In spite of all good intents to exclude patients with cardiac comorbidities at baseline and to adjust for potential confounders through sensitivity analysis, propensity score matching and stratification in hindsight, PWE varied significantly in vascular and lifestyle risk factors compared to those without epilepsy, casting doubt if the final association seen was indeed a direct effect of seizures to the heart. Moreover, the ASMs classification was based on their chemical properties rather than their mechanism of action, perhaps because of the multiple mechanism of actions of certain ASMs. Through that lens, medications that are notoriously linked with arrhythmias in clinical practice (eg, phenytoin) were not associated with them in this study, but when all sodium channel blockers were lumped, this anticipated association emerged. Information on doses, treatment duration, and compliance with ASMs was not available, and, hence, it is unclear if the administration of ASMs altogether was a proxy of disease activity. Individuals without epilepsy but on ASMs for other indications were excluded, although that may have provided a window of opportunity to differentiate the arrhythmogenic role of seizures versus ASMs. Finally, the final impact of the identified arrhythmias on mortality was not addressed.

Regardless, this study[3] provides robust evidence to corroborate the increased risk of cardiac arrhythmias in PWE. One should remember though that association does not automatically constitute causation. According to Hill's criteria,[4] many parameters such as the strength, the consistency, the specificity, the temporality, the biological plausibility, and, potentially, the reversibility of an epidemiological association are needed to establish a causative link, in addition to a dose–response relationship, experimental indications, and coherence between epidemiological and paraclinical evidence. The temporality of the association emerging from the current investigation[3] contributes to prior literature which supports some of these criteria. For example, consistency arises from another large community study from the Netherlands corroborating that epilepsy, particularly when symptomatic and not controlled, was associated with an increased sudden cardiac death risk, and so were ASMs, particularly sodium channel blockers, both among symptomatic epilepsy cases and nonepilepsy cases.[5] Some of the ASMs effect may stem from their metabolic effects to the cardiovascular system, particularly for cytochrome P450 inducers.[6] The biological plausibility hails also from the repeated catecholamine excess of chronic epilepsy resulting in myocyte vacuolization and interstitial fibrosis, accelerated atherosclerosis, and myocardial ischemia and stunning.[2] The paraclinical support stems from echocardiogram studies that have demonstrated higher left ventricle stiffness and greater left atrial volume in PWE compared to controls, particularly those PWE with indices of autonomic dysfunction and polytherapy with ASMs, including carbamazepine.[7]

In other words, there is enough smoke to suggest that the fire of the epileptic heart is indeed blazing. As health care providers, we cannot stay halfhearted about this; so, what is our fire prevention plan, our smoke detector, and our fire extinguisher? Obviously, controlling the seizures, if possible with ASMs exhibiting the least arrhythmogenic and metabolic effects, is a no brainer. Furthermore, performing at least basic structural (eg, echocardiogram) and functional (eg, electrocardiogram) screening in elderly patients or younger patients with known genetic or vascular risk factors, particularly if uncontrolled or in need of potentially arrhythmogenic ASMs, seems prudent.[8] Utilizing novel monitoring devices such as loop recorders[9] and wearables[10] for high-risk patients and providing their caregivers with the training and the equipment required to intervene in case of emergency takes heart, but could save lives. Finally, without skipping a beat, we need to expand our research efforts to get in the heart of this ostensible association between arrhythmias and epilepsy in order to fully elucidate its pathophysiology and identify the optimal diagnostic and therapeutic approach to tackle it.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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