Epilepsy Currents
2024, Vol. 24(2) 90-92

DOI: 10.1177/15357597231224652
journals.sagepub.com/home/epi
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The Interplay Between Epilepsy and Alzheimer's Disease: A Pas De Deux

Alzheimer Disease and Epilepsy: A Mendelian Randomization Study

Fang Y, Si X, Wang J, Wang Z, Chen Y, Liu Y, Yan Y, Tian J, Zhang B, Pu J. *Neurology*. 2023;101(4):e399-e409. doi:10.1212/WNL.0000000000207423. PMID: 37225432; PMCID: PMC10435057

Background and objectives: Observational studies suggested a bidirectional relationship between Alzheimer disease (AD) and epilepsies. However, it remains debated whether and in which direction a causal association exists. This study aims to explore the relationship between genetic predisposition to AD, CSF biomarkers of AD (β-amyloid [Aβ] 42 and phosphorylated tau [pTau]), and epilepsies with 2-sample, bidirectional Mendelian randomization (MR) method. Methods: Genetic instruments were obtained from large-scale genome-wide meta-analysis of AD ($N_{case/proxy} = 111,326$, $N_{control} = 677,663$), CSF biomarkers of AD (Aβ42 and pTau, N = 13,116), and epilepsy ($N_{case} = 15,212$, $N_{control} = 29,677$) of European ancestry. Epilepsy phenotypes included all epilepsy, generalized epilepsy, focal epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, generalized epilepsy with tonic-clonic seizures, focal epilepsy with hippocampal sclerosis (focal HS), and lesion-negative focal epilepsy. Main analyses were performed using generalized summary data-based MR. Sensitivity analyses included inverse variance weighted, MR pleiotropy residual sum and outlier, MR-Egger, weighted mode, and weighted median. Results: For forward analysis, genetic predisposition to AD was associated with an increased risk of generalized epilepsy (odds ratio [OR] 1.053, 95% CI 1.002-1.105, $p = 0.038$) and focal HS (OR 1.013, 95% CI 1.004-1.022, $p = 0.004$). These associations were consistent across sensitivity analyses and replicated using a separate set of genetic instruments from another AD genome-wide association study. For reverse analysis, there was a suggestive effect of focal HS on AD (OR 3.994, 95% CI 1.172-13.613, $p = 0.027$). In addition, genetically predicted lower CSF Aβ42 was associated with an increased risk of generalized epilepsy ($\beta = 0.090$, 95% CI 0.022-0.158, $p = 0.010$). Discussion: This MR study supports a causal link between AD, amyloid pathology, and generalized epilepsy. This study also indicates a close association between AD and focal HS. More effort should be made to screen seizure in AD, unravel its clinical implications, and explore its role as a putative modifiable risk factor.

Commentary

In the tapestry of the neurons, epilepsy and Alzheimer's disease (AD) emerge as enigmatic dancers, twirling through the corridors of the brain. Epilepsy, akin to an electric storm, disrupts the serene rhythm of brains. Amid this chaos, AD takes its subtle hold, eroding the pillars of memory. Together, they orchestrate a melancholic ballet. Indeed, the accumulating evidence for a bidirectional association between epilepsy and AD is undisputable.[1] Nevertheless, the cause-and-effect dilemma of this pas de deux continues to pose a challenge in neuroscience. The longstanding debate of the chronological relationship between the 2 diseases-whether one causes the other or if there is a shared underlying mechanism continues to be a subject of immense scientific discussion.[1]

To understand this paradox, Fang et al used a 2-sample Mendelian randomization (MR) to study whether epilepsy causes AD or AD causes epilepsy.[2] The causative impact of an exposure on an outcome can be approximated accurately using genetic variants utilized by MR. Thus, the authors attempted to answer several vital questions in this study.

Does AD drive focal epilepsy? Alzheimer's disease is associated with an 8-10-fold higher risk of developing focal epilepsy than the general population.[3] Up to 42% of AD without epilepsy show evidence of subclinical focal seizures and interictal epileptiform discharges (IEDs) on EEG.[1,3] It has been postulated that hippocampal dysfunction and hyperexcitability in AD ultimately give rise to mesial temporal lobe epilepsy (MTLE).[1,3] The authors add to the existing body of evidence by finding a causal link between genetic predisposition to AD and an increased risk of focal epilepsy with hippocampal sclerosis (HS) validated by replication analysis. Does that imply all AD with HS have focal epilepsy, or should they be treated? This causal association underscores the necessity for future studies explicitly focusing on the subpopulation of AD

with HS to understand the risk of developing epilepsy and its clinical implications. High-risk AD with HS may also be considered for early screening for epilepsy using prolonged EEG.

Does focal epilepsy drive AD? Recent multicenter longitudinal studies have shown an increased risk of incident dementia in focal epilepsy.[4] A randomized controlled trial showed that targeting subclinical hyperexcitability and IEDs by low-dose levetiracetam in AD may slow the disease progression.[5] Several mechanisms of how epilepsy may lead to dementia have been proposed. Some of these include chronic hippocampal network remodeling and tau accumulation and propagation.[3] However, causality has not been established in such prospective observational studies. By using MR, Fang et al took these findings one step further. They found a possible causal impact of focal epilepsy with HS on AD development, which was not replicable on the validation dataset. These findings suggest that aggressively controlling focal epilepsy with HS may help mitigate the risk of AD[5] or slow the progression of preexisting AD. However, more extensive studies are needed to confirm the replicability of these results.

Does AD drive generalized epilepsy? The literature on the association between AD and generalized epilepsy is scarce. While lifetime generalized-tonic-clonic seizures have been observed in >50% of AD, most are secondary to focal epilepsies.[1,6] Fifteen percent or less of AD patients have shown evidence of generalized epilepsy based on EEG.[1,6] This has been attributed to bilateral network hypersynchrony.[1,6] The most compelling evidence of an association between AD and generalized epilepsy comes from studies on late-onset generalized myoclonic epilepsy with Down syndrome (LOMED).[7] LOMED is intimately related to symptomatic AD in Down syndrome.[7] Therefore, the most novel finding of the current study is the identification of a causal association between AD and an increased risk of generalized epilepsy, which was validated on the replication dataset. However, a causal link was not found in the subsets of generalized epilepsies such as childhood absence or juvenile myoclonic epilepsies, likely because of the small sample size in each subset. These results emphasize the importance of dedicating special attention in forthcoming research not only to focal epilepsies but also to generalized epilepsies in the context of AD. In addition, there is a need to ascertain the extent to which AD influences different subtypes of generalized epilepsies.

What roles do amyloid and tau play? Described as the "*two faces*" of amyloid pathology,[8] there is an abundance of evidence of an association between amyloid pathology and epilepsy.[8] Animal models of epilepsy have shown higher levels of amyloid fibrils and lower levels of soluble amyloid beta (Aβ).[9] In humans, a decrease in plasma Aβ42/Aβ40 ratio is associated with a 2-fold increased risk of developing epilepsy.[10] Low cerebrospinal fluid (CSF) Aβ42 has also been reported in late-onset epilepsy (LOE).[8] The authors extend these findings and provide compelling evidence of low CSF Aβ42 and its causal link to generalized epilepsy. However, their analysis did not account for the APOEε4 allele, which has a robust association with amyloid burden and is also an important risk factor for LOE.[3] Therefore, subsequent MR studies should focus on examining the interaction between APOEε4, amyloid biomarkers, and epilepsy.

As for tau pathology, existing evidence suggests that higher CSF total Tau (t-Tau) is an independent predictor of developing epilepsy.[11] T-tau has even been postulated to be the primary driver of epilepsy.[3] The diagnostic value of phosphorylated-tau 181/t-tau in MTLE has also been demonstrated.[12] Tau may cause presynaptic glutamate release, increased synaptic transmission, decreased inhibitory current, and increased N-methyl-D-Aspartate (NMDA)-receptor-mediated dysfunction.[3] In turn, these may lead to neuronal hyperexcitability and seizures.[3] The authors found no causal link between phosphorylated-tau (p-Tau) and epilepsy and no impact of epilepsy on CSF biomarkers. However, they did not explore the association between t-Tau and epilepsy. In the context of AD and epilepsy, future MR studies should give additional consideration to t-tau and p-tau/t-tau ratios.

While the strengths of the current study include the MR method, sophisticated statistical techniques, and validation of results using sensitivity and replication analyses, some shortcomings warrant attention. The study is constrained by inconsistency in the diagnosis of AD dementia across various centers. The limited sample size of CSF samples and lack of biomarker confirmation of AD in many cases may have impacted the results of the study in an unpredictable fashion. No EEG data were analyzed by the authors despite the increasing evidence of electrophysiologic changes and IEDs in many AD patients. Using MR, the authors could not investigate the time-specific impact to understand whether epileptogenicity presents before AD onset or after it. Lastly, the study is only based on European ancestry and may not be widely applicable.

A causal association between AD and focal epilepsy with HS, AD, and generalized epilepsy, and low CSF Aβ42 and generalized epilepsy takes us many steps further and calls for action. There is a need for research on subpopulations of AD with HS and AD with generalized epilepsies. Screening high-risk AD with HS for early identification of epilepsy with EEG should be considered. Given the intimate link between the 2 diseases, future AD clinical trials should include AD with epilepsy. Lastly, future MR studies focusing on t-tau and p-tau/t-tau ratios and the interplay between APOEε4, amyloid pathology, and epilepsy are also warranted.

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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.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Alzheimer's Association and American Epilepsy Society.

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