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Late-Onset Epilepsy: A Distinct Entity that Begins and Ends With the Associated Comorbidities

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Late-Onset Epilepsy, Mortality, Elderly, Dementia, Stroke

Mortality in Patients With Late-Onset Epilepsy: Results From the Atherosclerosis Risk in Communities Study

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Background and Objectives: This study aims to determine the risk of mortality and causes of death in persons with late-onset epilepsy (LOE) compared to those without epilepsy in a community-based sample, adjusting for demographics and comorbid conditions. Methods: This is an analysis of the prospective Atherosclerosis Risk in Communities study, initiated in 1987–1989 among 15,792 mostly Black and White men and women in 4 US communities. We used Centers for Medicare & Medicaid Services fee-for-service claims codes to identify cases of incident epilepsy starting at or after age 67. We used Cox proportional hazards analysis to identify the hazard of mortality associated with LOE and to adjust for demographics and vascular risk factors. We used death certificate data to identify dates and causes of death. Results: Analyses included 9090 participants, of whom 678 developed LOE during median 11.5 years of follow-up after age 67. Participants who developed LOE were at an increased hazard of mortality compared to those who did not, with adjusted hazard ratio 2.39 (95% confidence interval 2.12–2.71). We observed excess mortality due to stroke, dementia, neurologic conditions, and end-stage renal disease in participants with compared to those without LOE. Only 4 deaths (1.1%) were directly attributed to seizure-related causes. Conclusions: Persons who develop LOE are at increased risk of death compared to those without epilepsy, even after adjusting for comorbidities. The majority of this excess mortality is due to stroke and dementia.

Commentary

With 1 in 6 people in the US being elderly (65 years or older), it is no secret that we live in a rapidly aging population. The elderly population is at the highest risk of epilepsy development (late-onset epilepsy [LOE]) compared to any other age group. Stroke is a well-known and most common underlying etiology of LOE. Additionally, people with dementia are 6–8 times more likely to develop LOE. Until recently, a large body of literature poorly differentiated between epilepsy in the elderly and LOE among the elderly. However, in the last few years, some remarkable research has shed new light on LOE. We have learned from longitudinal studies that the presence of hypertension, diabetes, *APOE* ε4 genotype, and MRI white matter hyperintensities in adulthood, even in the absence of evident stroke and dementia, significantly increase LOE risk.[1,2] Compared to their younger counterparts, people with LOE are significantly more likely to have chronic medical conditions and less often have learning disabilities and a family history of epilepsy.[3] Histopathological data support acquired causes as the predominant pathology underlying drug-resistant LOE.[4] This distinct etiopathogenesis suggests that LOE is not just about the late appearance of recurrent seizures but has fundamental differences compared to epilepsy in the younger age groups.

Additionally, recent data suggest that comorbidities like stroke and dementia are not just part of LOE's origin story but may also emerge later in the narrative. Individuals with LOE have close to 3 times the increased risk of subsequently developing stroke.[5] Similarly, the risk of dementia diagnosis after LOE increases by 2–3 times compared to elderly individuals who do not develop epilepsy.[6,7] This intertwining of LOE and comorbidities of stroke and dementia suggests a triangulated relationship between vascular, neurodegenerative, and epileptic pathologies.[8] With the confluence of such factors that are known contributors to increased mortality in the general population, it is only natural to wonder about the mortality risk among individuals with LOE and the associated causes of death, especially given its distinctive etiopathogenesis. The article by Johnson et al[9] reviewed here tries to answer these questions.

The study analyzed just over 9000 elderly individuals from the Atherosclerosis Risk in Communities (ARIC) study, a racially diverse cohort of 22% Black participants. Among them,

678 (7.4%) developed LOE during the prospective follow-up. As expected from the prior analysis of the same cohort, LOE individuals were significantly more likely to have hypertension, diabetes, and *APOE* ε4 genotype.[1] Overall, stroke and dementia were diagnosed in 24.5% and 42% individuals with LOE, respectively, compared to 9.6% and 16.6% of the non-LOE cohort. Slightly more than half (54%) of LOE individuals died during the follow-up compared to one-third (34.9%) of non-LOE counterparts. Before analyzing and interpreting the mortality risk among LOE compared to the non-LOE cohort, it is critical to understand the abovementioned intertwining of LOE with stroke and dementia. Either of them may act as a confounder when they occur before LOE because they increase the risk of exposure (LOE) as well as the outcome (death). However, when stroke or dementia is diagnosed after LOE, they may modify LOE's effect on mortality. The study found that the adjusted (for demographics, medical comorbidities, and prior stroke or dementia history) mortality risk was at least twice (hazard ratio [HR] 2.39 [2.12–2.71]) as high in LOE individuals who did not develop stroke or dementia after the epilepsy diagnosis. The risk was almost 3 times (HR = 3.11 [2.69–3.62]) as high when LOE individuals who never had stroke or dementia (before or after LOE) were compared to their non-LOE counterparts. This increase in mortality risk likely reflects a much healthier comparator group that lacks all 3 neurological conditions. Interestingly, due to the complex relationship between LOE, stroke, and dementia, although the analysis of the total study population found that the mortality risk remains significantly higher among LOE individuals than non-LOE cohort, the HR was not constant over time, that is, violated the proportional hazards assumption.

The analysis of the cause of death, based on ICD-9 and ICD-10 codes on the death certificate, revealed that stroke, dementia, and "other neurologic" (mostly Parkinson disease) and "other" (mostly end-stage renal disease) causes led to significantly higher deaths in LOE compared to the non-LOE cohort. Stroke and dementia combined accounted for a quarter of all deaths among LOE and a majority (56%) of excess deaths in this cohort. Despite significantly higher cardiovascular risk factors and death from cardiovascular causes being the leading cause of death among LOE, the statistical modeling did not reveal cardiovascular mortality to be significantly different between the 2 cohorts. Unlike younger PWE who have a multiple-times higher risk of deaths due to external causes like accidents compared to the non-epilepsy population, the current study found such causes comparable among the LOE and non-LOE cohort. Also, seizure-related deaths, which account for a large percentage of mortality in younger PWE, led to only 1.1% of LOE deaths.

The current study's biggest contribution is not as much in showing an increased risk of mortality among LOE, which is in line with similarly increased risk among PWE in younger age groups. Instead, it's that it highlights the differential causes of death in this age group compared to their younger counterparts. The clinical presentation of LOE is different than epilepsy in the younger age group.[3] The former less frequently have auras and generalized tonic–clonic seizures, which may be a contributory factor in the delay of epilepsy diagnosis among the elderly by almost 2 years.[10,11] Additionally, the seizures in LOE show relatively better anti-seizure medication (ASM) response.[12] When we consider the differences in causes of death in conjunction with clinical feature differences and the unique pathogenesis of epilepsy among the elderly, it seems that the current study's findings lend more credence to the assertion that LOE is a distinct epilepsy type.

Due to the limitation of relying on ICD codes from CMS Medicare data, the study cannot delve into important epilepsy-related features like seizure burden, duration, and ASM's association with mortality. These factors contribute to increased cerebrovascular and cardiovascular risk, which, in turn, elevates the risk of LOE, and thereby, mortality.[1,8] Therefore, it seems logical that early interventions to address the modifiable vascular risk factors could potentially break the vicious cycle of LOE, stroke, dementia, and death in our growing elderly population. Although the current study's findings need replication in other populations, it seems that we are at a point where emerging, robust scientific data with clear biological plausibility is signaling that LOE is a harbinger of increased stroke, dementia, and mortality risk. However, this poses a formidable challenge: how best to translate this accumulating knowledge into actionable information in routine clinical practice? Just the diagnosis of epilepsy at this late stage of life is usually quite surprising to the elderly and brings its associated uncertainty. In that context, what is the right time to also inform them about their substantially increased risk of stroke or dementia and, worse, death? Maybe, not on the very first visit. Should we triage every new LOE patient to the cerebrovascular clinic or back to their PCP for closer monitoring and treatment of vascular risk factors? What about starting antithrombotics? We lack definitive, evidence-based answers to any of these questions at the moment. Nonetheless, it seems that we are approaching the threshold of rapid expansion in our understanding of LOE. While such inflection points in knowledge may bring uneasiness due to the vast unknown, it should also fill us with the excitement about the meaningful difference that continued progress in this direction would make to the lives of individuals with LOE.

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