Solid Evidence for a Thin Hypothesis

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Progressive Cortical Thinning in Patients With Focal Epilepsy

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Importance: It is controversial whether epilepsy is a static or progressive disease. Evidence of progressive gray matter loss in epilepsy would support early diagnosis, rapid treatment, and early referral for surgical interventions. Objective: To demonstrate progressive cortical thinning in patients with focal epilepsy distinct from cortical thinning associated with normal aging. Design, Setting, and Participants: A case–control neuroimaging study was conducted from August 3, 2004, to January 26, 2016, among 190 patients with focal epilepsy at a tertiary epilepsy referral center (epilepsy data) and 3 independent comparison cohorts matched for age and sex (healthy volunteer data; n = 141). Exposures: Two or more high-resolution T1-weighted magnetic resonance imaging scans at least 6 months apart (mean [SD] interval, 2.5 [1.6] years). Main Outcomes and Measures: Global and vertexwise rate of progressive cortical thinning. Results: A total of 190 people with focal epilepsy (99 women and 91 men; mean [SD] age, 36 [11] years; 396 magnetic resonance imaging scans) were compared with 141 healthy volunteers (76 women and 65 men; mean [SD] age, 35 [17] years; 282 magnetic resonance imaging scans). Widespread highly significant progressive cortical thinning exceeding normal aging effects, mainly involving the bilateral temporal lobes, medial parietal and occipital cortices, pericentral gyri, and opercula, was seen in 146 individuals with epilepsy (76.8%; 95% CI, 58%-95%). The mean (SD) annualized rate of global cortical thinning in patients with epilepsy was twice the rate of age-associated thinning observed in healthy volunteers (0.024 [0.061] vs 0.011 [0.029] mm/y; $P = .01$). Progression was most pronounced in adults older than 55 years and during the first 5 years after the onset of seizures. Areas of accelerated cortical thinning were detected in patients with early onset of epilepsy and in patients with hippocampal sclerosis. Accelerated thinning was not associated with seizure frequency, history of generalized seizures, or antiepileptic drug load and did not differ between patients with or without ongoing seizures. Progressive atrophy in temporal (n = 101) and frontal (n = 28) lobe epilepsy was most pronounced ipsilaterally to the epileptic focus but also affected a widespread area extending beyond the focus and commonly affected the contralateral hemisphere. For patients with temporal lobe epilepsy, accelerated cortical thinning was observed within areas structurally connected with the ipsilateral hippocampus. Conclusions and Relevance: Widespread progressive cortical thinning exceeding that seen with normal aging may occur in patients with focal epilepsy. These findings appear to highlight the need to develop epilepsy disease-modifying treatments to disrupt or slow ongoing atrophy. Longitudinal cortical thickness measurements may have the potential to serve as biomarkers for such studies.

Commentary

The question of whether epilepsy is a static or dynamic process has been a subject of debate since Gowers proclaimed that "seizures beget seizures." Is epilepsy a progressive disease? That was part of the title for an *Epilepsia* review in 2000.[1] That paper concluded that the answer is complicated and depends in part on how we define disease progression. Fast forward to 2017 when a meta-analysis examining whether progressive atrophy is demonstrated in intractable temporal lobe epilepsy (TLE) stated as a preamble that "It remains unclear whether drug-resistant temporal lobe epilepsy (TLE) is associated with cumulative brain damage, with no expert consensus and no quantitative syntheses of the available evidence."[2] The conclusion of this meta-analysis was that while the neuroimaging literature is overall suggestive of progressive atrophy in drug-resistant TLE, published studies have not employed robust enough designs to directly demonstrate it. The authors exhorted investigators to employ longitudinal multicohort studies to unequivocally differentiate atrophy due to normal aging from epilepsy disease progression.

Galovic et al have answered the call with a longitudinal study of a cohort with epilepsy compared to 3 cohorts without epilepsy. The authors studied 190 patients with focal epilepsy and 141 age and gender-matched healthy controls. All patients

and controls had at least 2 high-resolution T1-weighted magnetic resonance imaging (MRI) scans performed on the same scanner at least 6 months apart. Cortical thickness was estimated using the projection-based thickness method in the fully automated and validated Computational Anatomy Toolbox (CAT12). Annualized cortical thinning was determined by subtracting vertexwise thickness values of aligned baseline and follow-up MRI scan pairs and dividing by the interscan interval. This step obviated the need of finding patients and controls with the exact interscan interval. To analyze whether the spatial patterns of progressive cortical thinning reflected areas of connectivity to the epileptic focus, the authors performed a set of connectivity analyses with probabilistic tractography based on 10 high-quality diffusion data sets from BCBtoolkit. This analysis was accomplished for the TLE subgroup because the seed location (ie, hippocampus) is a well-established and well-defined location of the epileptogenic zone in most cases of TLE. A similar analysis could not be made for extra-TLE because of the high variability of epileptogenic foci location(s). People with epilepsy had a higher mean yearly rate of global cortical thinning compared with healthy volunteers ($P = .01$), with greater thinning associated with increasing age. A total of 76.8% of people with epilepsy in their cohort showed progressive cortical thinning that was distinct from that seen with normal aging. Cortical thinning was *not* associated with seizure frequency, number of antiepileptic drugs taken, or history of secondarily generalized seizures. In the TLE subgroup, accelerated cortical thinning was seen in functionally connected areas.

The current study's main strengths are the large N and the use of longitudinal data for both patient and control cohorts in an age- and gender-matched fashion. Several previous studies demonstrating cortical thinning in patients with focal epilepsy reached limited conclusions because of the cross-sectional nature of data analyzed[3] or the lack of age- and gender-matched controls.[4,5] A cross-sectional design confounds between- and within-subject effects and, thus, does not directly address progression. Moreover, it does not permit a direct control of aging-related effects, as chronological age and epilepsy duration are highly correlated.[2] The current study design allowed Galovic et al to demonstrate that the cortical changes seen in patients with focal epilepsy are different than those seen in normal healthy controls, are not age-related, and progress over time.

The finding that cortical atrophy in the TLE subgroup was more pronounced in functionally connected areas has implications beyond the study of disease progression. These results appear to further support the concept that focal epilepsy is a network disease process[6] and adds a structural component to buttress a hypothesis that is mostly supported by electrophysiologic and functional imaging data.

It must be noted that some of the other findings in the Galovic et al's study do differ from earlier studies and will need to be replicated and validated. Coan et al[7] compared a cohort of patients with TLE to a cohort of normal controls in a longitudinal voxel-based morphometry study and found that a higher frequency of seizures and a longer duration of epilepsy were associated with progression of gray and white matter atrophy in patients. Liu et al[8] used image subtraction analysis on a prospective longitudinal study on patients with chronic epilepsy and newly diagnosed epilepsy and found that age and multiple antiseizure drug exposure were associated with neocortical atrophy. While it may be tempting to speculate that the superior design of the Galovic et al study leads to more valid results, only further studies will ultimately provide the answers.

If validated, the finding that progressive cortical atrophy in patients with epilepsy was not associated with disease severity or duration is significant on a couple of levels. First, if seizure frequency, seizure severity, or the number of antiseizure drugs trialed has no effect on cortical thinning, this suggests that effective pharmacologic interventions to stop or minimize seizures are not likely to influence the loss of gray matter. Thus, a major part of what clinicians feel is successful treatment of patients with epilepsy (ie, achieving seizure freedom) appears to have no bearing on a process that is decreasing overall brain health. Would a surgical "cure" of epilepsy be more effective in stopping neuronal degeneration? The preliminary data are not reassuring. One recent study suggests there is ongoing contralateral hippocampal atrophy after successful anterior temporal lobe surgery.[9] Second, these findings appear to overturn the traditional thinking that epilepsy is a progressive disease because of the damaging effects of continued seizures.[1,10] If the *absence* of ongoing seizure activity does not stop the progressive cortical atrophy seen in patients with epilepsy, we will be forced to consider that the neuronal damage is secondary to other etiologies such as low-level inflammation or an autoimmune process, to name just two of many speculative possibilities. This would certainly produce a paradigm shift in a field which has long regarded seizure activity as the main driver of adverse cognitive sequelae in patients with nonsyndromic focal epilepsy.

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