EARLY SEIZURE ONSET AND BRAIN DEVELOPMENT: THE EMERGING PICTURE

Total Cerebral Volume is Reduced in Patients with Localization-Related Epilepsy and a History of Complex Febrile Seizures

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CONTEXT: Febrile seizures may lead to later epilepsy. They have been associated with hippocampal atrophy but their effect on total cerebral volume is unknown.
OBJECTIVE: To compare total cerebral volume in patients with mesial temporal lobe epilepsy with and without a history of complex febrile seizures (CFS).
DESIGN: Survey.
SETTING: Epilepsy monitoring center.
SUBJECTS: Forty patients with localization-related epilepsy and temporal lobe onset determined by video electroencephalogram and 20 controls.
INTERVENTION: Magnetic resonance imaging measurement of cerebral volume.
MAIN OUTCOME MEASURE: Total cerebral volume.
RESULTS: Patients with a history of CFS had significantly reduced total cerebral volume compared with patients without CFS. In addition, male patients with CFS had significantly lower total cerebral volume than male normal controls. There was no significant difference between patients without CFS, or all patients, and controls.
CONCLUSION: Complex febrile seizures may have a global effect on brain development.

The Neurodevelopmental Impact of Childhood-onset Temporal Lobe Epilepsy on Brain Structure and Function

Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, Wendt G, O'Leary D, Magnotta V

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PURPOSE: To characterize the neurodevelopmental correlates of childhood-onset temporal lobe epilepsy on brain structure and cognition compared with late-onset chronic temporal lobe epilepsy and healthy controls.
METHODS: Healthy controls ($n = 62$) and patients with early ($n = 37$) versus late ($n = 16$) age at onset of temporal lobe epilepsy were compared with high-resolution quantitative magnetic resonance imaging (MRI) volumetrics and comprehensive neuropsychological assessment.
RESULTS: Patients with childhood-onset temporal lobe epilepsy (mean onset age, 7.8 years) exhibited widespread compromise in neuropsychological performance and substantial reduction in brain tissue volumes extending to extratemporal regions compared with healthy controls and late-onset temporal lobe epilepsy patients (mean onset age, 23.3 years). Most evident was reduced total white-matter volume among the childhood-onset patients. Reduction in brain tissue volume, especially total white-matter volume, was associated with significantly poorer cognitive status, attesting to the clinical significance of the volumetric abnormalities.
CONCLUSIONS: Childhood-onset temporal lobe epilepsy appears to be associated with an adverse neurodevelopmental impact on brain structure and cognition that appears generalized in nature and especially evident in white-matter tissue volume.

COMMENTARY

The impact of recurrent seizures on brain structure, function, and development constitutes a central, yet unresolved, issue in clinical epileptology. Correlations between recurrent seizures in the developing brain and adverse effects on structure and function have been described. However, establishing a causal relationship remains difficult, in part, because of formidable methodological challenges posed by confounding variables, such as underlying substrate, age, and number or type of medications. Two recently published studies (Hermann, et al. and Theodore, et al.) evaluate the correlation between brain volume and both brain structure and neuropsychological status in patients with early onset of recurrent seizures.

The research by Hermann, et al. specifically assesses the variable of age at onset, examining brain structure and development in patients with temporal lobe seizures. By comparing healthy controls to individuals with both early and late seizure onset, the investigators showed that early, but not late, seizure onset is associated with reduced brain tissue volume, particularly total white matter volume. Even late-onset patients with a history of chronic temporal lobe epilepsy had considerably fewer volumetric and cognitive abnormalities than early-onset patients. The reported reductions in brain volume are associated with significantly poorer cognitive status and a generalized reduction in neuropsychological function. The study was carefully designed, and its conclusions are supported by the research of Theodore et al., who examined cerebral volume in patients with localization-related epilepsy and a childhood history of complex febrile seizures. Similarly, Theodore and colleagues found that compared to neurologically normal controls, subjects with childhood complex febrile seizures had significantly decreased total cerebral volume—but only in men, not in women. Unlike in the Hermann, et al. study, Theodore and coworkers found that patientswith a history of complex febrile seizures did *not* have lower scores on neuropsychologicaltests (with the exception of the Boston Naming Test).

Two critical findings were shared by both studies. First, the duration of seizures showed no correlation with the amount of tissue loss. And second, tissue loss routinely occurred in brain regions outside the primary seizure focus. These results implicate global neurodevelopmental consequences of early seizure onset. They provide a rationale for understanding impairments in cognitive domains attributed to brains regions distant from the seizure focus or to global deterioration or dementia, which may occasionally accompany chronic epilepsy. Furthermore, the results of both studies underscore the critical importance of age at seizure onset, rather than absolute number of seizures or seizure duration.

While these findings are of considerable interest, the story is far from complete and far more complex than presented here. For example, other studies have corroborated the relationship between chronic epilepsy and tissue loss, but in contrast, report that up to 39% of newly diagnosed epilepsy patients exhibited neocortical atrophy at presentaion (1). Thus, it is unclear why some patients show early cellular changes, whereas it is a late finding in others. Furthermore, a causal relationship has already been established between *continuing* seizures, not age of onset, and a decline in hippocampal volume for discrete clinical conditions, such as hippocampal sclerosis and medically resistant temporal lobe epilepsy (2). How are these differences to be reconciled? It is, thus, probable that from a damage standpoint, all seizures are not equal or, alternatively, that some form of interaction between the seizure and its neurobiological substrate has a deterministic role in how or whether damage will occur. Growing evidence, therefore, suggests that both regional and global outcomes manifest through a variety of mechanisms. Specific factors, such as age of seizure onset and seizure localization, may provide an important starting point for further inquiry.

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References

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