A population-based longitudinal volumetric MRI study in Epilepsy

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Synopsis

Whether cerebral damage results from epileptic seizures remains a contentious issue. We report on the first longitudinal community-based quantitative MRI study to investigate the effect of seizures on the hippocampus, cerebellum and neocortex. Automated and manual measurement techniques were used to identify changes in brain volume in patients with chronic epilepsy, newly diagnosed seizures and control subjects who underwent two magnetic resonance imaging (MRI) brain scans 3.5 years apart. Overall, rates of hippocampal and cerebral atrophy were primarily determined by age and were not significantly different between the three subject groups.

Introduction

Chronic intractable epilepsy is associated with structural alterations in brain morphology [1]. The timing of such changes in relation to disease onset and progression remains obscure. Inferences on causality that can be drawn from cross-sectional studies are necessarily limited, and comparison of structural changes and seizure frequency in such studies have yielded contradictory findings [2-3]. We aimed to investigate the effect of epileptic seizures on hippocampal, cerebral grey and white matter and cerebellar volumes, by performing a population-based longitudinal MRI study. We sought to determine whether damage occurred at the early stages of the condition or following years of repeated seizures and intractable epilepsy.

Methods

153 patients with chronic active epilepsy, 90 patients with newly diagnosed seizures and 90 age-and sex-matched control subjects were prospectively recruited from a local population of 207,553. Subjects were scanned on a 1.5-T GE Signa Horizon Echospeed MR scanner (GE Medical Systems, Milwaukee, WI). Three experienced epileptologists classified patients at the time of recruitment according to epilepsy syndrome based on seizure semiology and EEG findings. Of the original cohort, 122 patients with chronic active epilepsy, 68 patients with newly diagnosed seizures and 90 controls were subjected to the follow-up assessment: scanning performed on the same MRI scanner using identical MRI acquisition sequences to the baseline imaging protocol (see below) and clinical data collection.

Qualitative assessment of scan pairs were performed on T1-weighted images, T2-weighted images, proton density images and 5mm thick coronal FLAIR images. Volumetric measurements were derived from a T1-weighted three-dimensional volumetric inversion recovery prepared spoiled gradient echo (IR-SPGR) sequence with 124 contiguous coronal partitions, 1.5mm thickness, a 24 x 18-cm field of view, matrix size 256 x 192, and 25 degree flip angle. Prior to volumetry, baseline and repeat T1-weighted volume datasets were corrected for signal inhomogeneity. The automatic segmentation software program, Exbrain was used to extract the brain and cerebrospinal fluid in the non-uniformity corrected baseline scan [4-5]. The repeat scan was coregistered and intensity matched to the segmented baseline scan using MRreg [6]. The optimum match was determined through maximising the cross-correlation of brain voxel intensities with a nine-parameter rigid body transformation. The coregistered repeat scan was subsequently resampled using sinc interpolation and a final segmentation applied. Exbrain was used to segment the coregistered image pairs, generating baseline and repeat values for total brain volume (TBV), grey matter volume (GMV), white matter volume (WMV) and intracranial volume (ICV) [5]. All measurements were performed by a single trained operator, using the volumetry tool in MRreg. Contiguous slices of matched datasets were displayed side-by-side, with the operator blinded to the clinical status of the subject and to the chronological order of the scan pairs [7-8]. Cerebellar volumetry was semi-automated and performed on the matched segmented T1-weighted images using seeds and region growing on brain segmented images. Two senior neuroradiologists, blinded to all clinical information, compared baseline and repeat images (without registration) for qualitative change.

Results

Baseline hippocampal, neocortical and cerebellar volumes were significantly different between the three groups, being lowest in the chronic epilepsy group and highest in the controls. The differences could be attributed to antecedent neurological insults. Overall, rates of hippocampal and cerebral atrophy were primarily determined by age and were not significantly different between the three subject groups. A history of a prior neurological insult was associated with an increased rate of cerebral atrophy (TBV), grey matter volume (GMV), white matter volume (WMV) and intracranial volume (ICV). There was considerable heterogeneity within the patient groups. Frequency of documented seizures, duration of epilepsy, antiepileptic drug use, status epilepticus, and gender had no effect on brain volumes.

Discussion and Conclusions

Methodologically, our approach to volumetry based on image registration, blinding and side-by-side display, improved the variability of repeated measurements. The heterogeneity of the patient group studied limits the inferences that can be made for specific syndromes and etiologies. However, the broad patient population allowed us to assess damage in the first few years following seizure onset. The methods used in this work are not designed to detect and quantify subtle and/or focal neocortical changes, which are the subject of a separate report.

In summary, overt structural cerebral damage is not an inevitable consequence of epileptic seizures. In general, brain volume reduction observed in epilepsy is the cumulative effect of an initial precipitating injury followed by age-related cerebral atrophy. Longer periods of observation may be needed to observe subtle effects of seizures. Early neurological insults may prime the brain, making it more vulnerable to the effect of ageing and seizures.

References