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Predictive value of hippocampal internal architecture asymmetry in temporal lobe epilepsy

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Summary
Background: Asymmetry of hippocampal internal architecture (HIA) clarity has been suggested to be a sign of hippocampal sclerosis (HS) and is frequently associated with other MRI findings of HS. The goal of this work is to use a previously developed HIA visual scoring system (Ver Hoef et al., 2013) to quantify HIA asymmetry in a retrospective series of consecutive temporal lobe epilepsy (TLE) patients and evaluate its value in predicting laterality of seizure onset both in patients with other signs of HS (HS+) and those without (HS—).
Methods: The HIA scoring system was used to rate hippocampal asymmetry and to assess the agreement between HIA and seizure lateralization. The median values of the average HIA scores for each hippocampus were compared for HS+ epileptogenic hippocampi, HS— epileptogenic hippocampi, and non-epileptogenic hippocampi with a Kruskal—Wallis one-way analysis of variance by ranks. Pair-wise differences between groups were evaluated with the two-tailed Mann—Whitney *U* test. A logistic regression model examined the utility of average HIA asymmetry score in predicting the true laterality of seizure onset as determined by video-EEG. Sensitivity and specificity are calculated using various asymmetry thresholds in each patient group.
Results: Fifty-five patients were identified who met inclusion criteria. Thirteen patients (24%) were found to have hippocampal atrophy and/or signal abnormality indicative of HS (HS+) and 42 did not (HS—). Significant differences were observed in the distribution of individual and average HIA scores between each of the groups of hippocampi, with HS+ hippocampi having the lowest HIA scores and non-epileptogenic hippocampi having the highest. Logistic regression analysis

Abbreviations: HIA, hippocampal internal architecture; HS, hippocampal sclerosis; TL, Etemporal lobe epilepsy; HS+, hippocampal sclerosis positive; HS—, hippocampal sclerosis negative.

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showed that the average HIA asymmetry score was a strong predictor of the laterality of seizure onset ($\beta = 3.93508$, $p < 0.001$). HIA asymmetry remained significant even after adjustment for HS+/HS− status ($\beta = 3.8854$, $p < 0.001$). Among HS− patients, when the average HIA asymmetry score was equal to or exceeded a threshold value of 0.5, the specificity for correctly predicting the side of seizure onset was between 95% and 100% with a sensitivity of 40—45%. Among HS+ patients, a threshold of 0.3 yielded a sensitivity of 85% and specificity of 100%.

Conclusions: In this report we show for the first time that HIA asymmetry is a significant predictor of the laterality of seizure onset in TLE patients with otherwise normal MRI findings, and that the proposed HIA scoring system has high specificity and moderate sensitivity for lateralizing seizure onset in patients with TLE.

Introduction

The hippocampus is the most frequently epileptogenic area of the human brain. As such, identification of a structural abnormality of the hippocampus on MRI is an important finding in the epilepsy patient, particularly if that patient is being evaluated for epilepsy surgery. The most frequently encountered hippocampal abnormality in epilepsy patients is hippocampal sclerosis (HS) (Margerison and Corsellis, 1966). The classic hallmarks of HS on MRI are atrophy and signal hyperintensity on T2-weighted or FLAIR images (Jackson et al., 1993). The presence of either of these findings is a strong indicator of hippocampal pathology and portends an excellent prognosis for a seizure-free outcome after surgical resection of the hippocampus (Radhakrishnan et al., 1998). Loss of hippocampal internal architecture clarity has been suggested as a third hallmark of HS (Jackson et al., 1993, 1994). Hippocampal internal architecture (HIA) as it is used here refers to the laminar structure of the body of the hippocampus that has a spiral appearance in the coronal plane due to the apposing layers of gray and white matter that define Ammon's horn (Ver Hoef et al., 2013). Loss of HIA has been reported to be present in a large majority of patients with other findings of HS (Jackson et al., 1994; Howe et al., 2010). However, previous studies of HIA asymmetry have been almost entirely in patients with other MRI evidence of HS, and therefore the value of HIA asymmetry as an independent biomarker of the epileptogenic hippocampus in the absence of atrophy or signal abnormality has not been shown heretofore. The purpose of this work is to determine if asymmetric loss of HIA has value in predicting the laterality of seizure onset in TLE patients. We have developed a simple scoring system for rating HIA clarity (Ver Hoef et al., 2013) to allow for statistical analysis of HIA clarity and its asymmetries. In this report we describe the HIA clarity scores of both the epileptogenic (ipsilateral to the side of seizure onset) and non-epileptogenic (contralateral to the side of seizure onset) hippocampi of a series of TLE patients and assess the sensitivity and specificity of this rating scheme for predicting the laterality of seizure onset based on the results of video-EEG monitoring.

Methods

After IRB approval was obtained, our epilepsy and MRI databases were reviewed to retrospectively find consecutive patients who had an MRI scan done according to our temporal lobe protocol on a Philips Achieva 3T scanner (Eindhoven, Netherlands) from 2004 through 2008 who also had a positive video-EEG study with ictal evidence of unilateral temporal lobe epilepsy. Patients with only inter-ictal abnormalities suggestive of TLE were not included to ensure that the diagnosis of unilateral TLE was as certain as possible. The images used for analysis were from a high-resolution T2-weighted TSE sequence with slices oriented in the oblique coronal plane orthogonal to the long axis of the body of the hippocampus to optimally view the hippocampal body in cross-section. This sequence used the following imaging parameters: TR 3000/TE 110/flip angle 90/NEX 2/FOV 240 mm/acquisition matrix 912 × 912/reconstruction matrix 1024 × 1024/slice 3 mm/gap 1 mm. Patients with MRI scans with significant movement artifact were excluded. Both patients with and without hippocampal atrophy or signal abnormality were included. The presence or absence of atrophy or signal abnormality was determined based on visual inspection by a board-certified neurologist (LV) with additional fellowship training and certification in neuroimaging (American Society of Neuroimaging and United Council of Neurologic Subspecialties) with over 7 years of experience interpreting clinical MRI scans as the physician of record. Quantitative hippocampal volumetry was not performed. Images were anonymized so the reviewer was blinded to patient identity and laterality of seizure onset.

For each patient, each slice through the hippocampal body was scored on each side according to our HIA rating scale starting with the first slice posterior to the hippocampal head and continuing until the upward turn of the tail produced noticeable through-plane volume averaging effects. A single rater (LV) scored the scans of all patients. Our HIA rating scale is described in detail in our companion paper and has been reported to have good inter-rater reliability among experienced reviewers (Ver Hoef et al., 2013). In brief, this rating system is based on visual assessment of HIA clarity and allows the reviewer to assign a score from ''1'' to ''4'' to a single hippocampal image with a ''4'' indicating excellent internal architecture differentiation and a ''1'' indicating no perceptible internal architecture. All scores were generated by a single reviewer. These individual scores for each side in each slice will be referred to simply as ''HIA scores''. For each hippocampus in each patient, the HIA scores on a given side were averaged across all the slices to produce an ''average HIA score'' for each hippocampus. Then, an average HIA asymmetry score was calculated for