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Hippocampal internal architecture and postoperative seizure outcome in temporal lobe epilepsy due to hippocampal sclerosis

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ABSTRACT

Purpose: Semi-quantitative analysis of hippocampal internal architecture (HIA) on MRI has been shown to be a reliable predictor of the side of seizure onset in patients with temporal lobe epilepsy (TLE). In the present study, we investigated the relationship between postoperative seizure outcome and preoperative semi-quantitative measures of HIA.

Methods: We determined HIA on high in-plane resolution preoperative T2 short tau inversion recovery MR images in 79 patients with presumed unilateral mesial TLE (mTLE) due to hippocampal sclerosis (HS) who underwent amygdalohippocampectomy and postoperative follow up. HIA was investigated with respect to postoperative seizure freedom, neuronal density determined from resected hippocampal specimens, and conventionally acquired hippocampal volume.

Results: HIA ratings were significantly related to some neuropathological features of the resected hippocampus (e.g. neuronal density of selective CA regions, Wyler grades), and bilaterally with preoperative hippocampal volume. However, there were no significant differences in HIA ratings of the to-be-resected or contralateral hippocampus between patients rendered seizure free (ILAE 1) compared to those continuing to experience seizures (ILAE 2-5).

Conclusions: This work indicates that semi-quantitative assessment of HIA on high-resolution MRI provides a surrogate marker of underlying histopathology, but cannot prospectively distinguish between patients who will continue to experience postoperative seizures and those who will be rendered seizure free. The predictive power of HIA for postoperative seizure outcome in non-lesional patients with TLE should be explored.

1. Introduction

Hippocampal sclerosis (HS) is the primary neuropathological correlate and most common cause of refractory mesial temporal lobe epilepsy (mTLE). The preoperative identification of HS is associated with an improved postoperative seizure outcome relative to patients with suspected TLE and no MRI lesion [1,2]. However, approximately 40% of patients with unilateral mTLE and HS will continue to experience debilitating postoperative seizures after short (i.e. 1–2 years) follow-up periods [2,3]. This figure may extend substantially when any kind of postoperative seizure is considered [3] or when long (i.e. >10 years) postoperative follow up periods are used [4]. It is unknown why such a large proportion of seemingly excellent candidates are not successfully rendered seizure free after temporal lobe surgery. Bitemporal epileptiform contributions remain a possible cause of persistent postoperative seizures; our recent findings indicate that groups of patients with persistent postoperative seizures have significant alterations of

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bilateral thalamohippocampal structural networks relative to patients surgically rendered seizure free [5,6]. Other work supports the hypothesis that, as a group, patients with residual postoperative seizures have increased contralateral hippocampal structural atrophy relative to patients with an optimal outcome [7,8]. Whilst these morphometric findings are novel and fit well with known epileptiform networks in mTLE, they do not permit the prospective classification of individual patients according to outcome. An imaging marker that can stratify patients according to outcome and can be easily incorporated into presurgical evaluation would represent an important tool.

Hippocampal volume is not a consistent reliable marker of postoperative outcome in patients with mTLE and HS [9]. It is therefore plausible to consider other imaging features of the hippocampus that may have predictive value. Semi-quantitative assessment of internal hippocampal architecture (HIA) has been shown to be a significant predictor of the laterality of seizure onset in TLE [10,11]. Changes in HIA have been reported in patients with histopathologically proven HS in whom no MRI-determined hippocampal atrophy was evident [12]. Loss of normal HIA is thought to be due to neuronal cell loss and replacement of the normal anatomical layers with gliotic tissue [13]. One primary advantage of semi-quantitative assessment of HIA is the potential ease of implementation into radiological evaluation for prospective patients being considered for surgery. We sought for the first time to assess the significance of preoperative HIA of the to-be-resected and contralateral hippocampi on short-term (1–3 years) postoperative seizure outcome in patients with mTLE. We additionally investigated the relationship between HIA and histopathological alterations of resected hippocampi and conventionally acquired hippocampal volumes.

2. Methods

2.1. Patients

Detailed demographic, clinical and preoperative workup information for patients studied in this investigation is described in our recent papers [5,6]. All patients were recruited and investigated at University Hospital Bonn, had presumed unilateral mTLE by virtue of seizure semiology and electrophysiological investigations, had neuroradiologically defined ipsilateral HS, and no evidence of bilateral HS or a secondary lesion that may be epileptogenic in nature. All patients were consecutively recruited on the basis of the above criteria between 2006 and 2011. Of 115 patients with mTLE and HS being enrolled into this study, 87 patients underwent selective amygdalohippocampectomy between 2006 and 2012 and received standardised postoperative follow up and outcome assessment using the International League Against Epilepsy (ILAE) outcome classification system [14].

2.2. Histopathological assessment

We determined ILAE [15] and Wyler [16] semi-quantitative gradings of HS from resected specimens. ILAE ratings included specimens with severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions (ILAE type 1), predominantly in CA1 (ILAE type 2), predominantly in CA4 (ILAE type 3) or with no HS. Wyler grades provided grades of overall hippocampal cell loss ranging from no pathology to Grade 4, with three incremental grades (mild, moderate, moderate to marked, and marked). Furthermore, quantitative neuronal cell density (number of neurons/μm^2) was obtained from each specimen, as recently described [17]. After scanning of Neu-N immunohistochemistry using a Mirax scanner (3DHistech, Hungary), rectangular regions-of-interest (ROIs) within hippocampal subfields CA1-4 were selected. NeuN-positive cells within these ROIs were counted with a quantitative software solution (HistoQuant, 3DHistech, Hungary) after manual control of correct cell identification.

2.3. MRI

All patients underwent MRI at the Life & Brain Center in Bonn on a 3 Tesla scanner (Magnetom Trio, Siemens, Erlangen, Germany) using an 8-channel head coil. For the assessment of HIA, we acquired a T2 short tau inversion recovery (STIR) sequence in the coronal plane angulated perpendicular to the long axis of the hippocampus (40 slices, TR = 5600 ms, TI = 100 ms, TE = 18 ms, resolution 0.45 × 0.45 × 2.0 mm, flip angle 0°). We determined hippocampal volume from 3D T1-weighted MPRAGE images acquired for each patient (160 slices, TR = 1300 ms, TI = 650 ms, TE = 3.97 ms, resolution 1.0 × 1.0 × 1.0 mm, flip angle 10°).

HIA was visually assessed using the HIA rating scale as described previously [10,11] on consecutive coronal T2-STIR sections in a rostral to caudal direction. All ratings were performed blind to diagnosis. The anterior limit of HIA assessment was taken as the first slice in which the uncus detaches from the hippocampal head and forms the hippocampal body, at which point the uncus is no longer visible. The posterior limit of HIA assessment was taken as the first slice in which the inferior and superior colliculi come clearly into view. Each hippocampal image was graded with a HIA score from '1' indicating no perceptible internal architecture to '4' indicating excellent internal architecture differentiation. Fig. 1 provides examples of coronal sections illustrating HIA scoring in patients investigated in the present study. HIA scores were based on assessment of the laminar appearance of apposing gray and white matter arising from the structure of Ammon's horn, giving rise to a dark hypointense band depicted in coronal sections. Left and right hippocampi were rated independently blind to patient identification and outcome information. An average HIA score was determined for each hippocampus in each patient, and a HIA asymmetry score was then determined by subtracting the left average HIA score from the right [10]. Using this approach, a positive HIA asymmetry score indicated preferential loss of HIA clarity on the ipsilateral (to-be-resected) side and a negative HIA asymmetry score indicated preferential loss on the contralateral side. Intra- (one rater, SE) and inter- (two raters, SE and SSK) rater reliability studies were performed on ten participants from the main cohort. These ten participants were randomly selected with no knowledge of diagnosis, including side of HS. Reliability studies indicated high levels of repeatability (intra-rater intraclass coefficient, two-way mixed model for consistency (ICC): left HIA = 0.97, right HIA = 0.98) and reproducibility (ICC: left HIA = 0.94, right HIA = 0.93). We additionally determined hippocampal volume from T1-weighted MPRAGE images using our previously described and well-validated approach that employed stereology in conjunction with point counting [18,19].

2.4. Statistical analysis

We used SPSS (IBM SPSS Statistics, Version 21.0, Armonk, NY) for statistical analysis. To determine differences between patient groups, a univariate ANOVA was used including group (seizure free vs persistent seizures; history of childhood febrile seizures vs no history) and HIA score, neuronal density and hippocampal volume as dependent variables. Seizure freedom was defined as an International League Against Epilepsy score of I (ILAE 1), and persistent postoperative seizures defined as ILAE 2–6 [14]. Chi-square tests were used to determine whether histopathological gradings and a history of childhood febrile convulsions were related to HIA and seizure outcome. Pearson's Correlation Coefficients were used to investigate relationships between