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Clinical factors predict surgical outcomes in pediatric MRI-negative drug-resistant epilepsy

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ABSTRACT

Purpose: Lack of a potentially epileptogenic lesion on brain magnetic resonance imaging (MRI) is a poor prognostic marker for epilepsy surgery. We present a single-center series of childhood-onset MRI-negative drug-resistant epilepsy (DRE) and analyze surgical outcomes and predictors.
Methods: Children with MRI-negative DRE who had resective surgery from January 2007 to December 2013 were identified using an institutional database. Relevant clinical, neurophysiological, imaging, and surgical data was extracted. The primary outcome measure was seizure freedom. Predictors of seizure freedom were obtained using multivariate logistic regression.
Results: Out of 47 children with MRI-negative DRE, 12 (25.5%) were seizure free (International League Against Epilepsy [ILAE] outcome class I), after mean follow-up of 2.75 (±1.72) years. Seizure-free proportion was significantly higher in patients with single seizure semiology and concordant ictal EEG (50.0% vs. 15.2%, $p = 0.025$). Multivariate analysis using only non-invasive pre-surgical data showed that children with daily seizures (OR 0.02, 95% CI < 0.001–0.55), and earlier onset of seizures (OR 0.72, 95% CI 0.52–0.99) were less likely to be seizure-free. Also, each additional anti-epileptic drug (AED) tried before surgery decreased the probability of seizure-free outcome (OR 0.16, 95% CI 0.04–0.63). Repeat multivariate analysis after including surgical variables found no additional significant predictors of seizure-freedom. Cortical dysplasia (ILAE type IB) was the commonest histopathology.
Conclusion: Surgical outcomes in children with MRI-negative DRE are determined by clinical factors including seizure frequency, age of onset of seizures, and number of failed AEDs.

1. Introduction

Identification of an epileptogenic lesion on brain magnetic resonance imaging (MRI) in people with drug-resistant epilepsy (DRE) is a robust predictor of successful epilepsy surgery [1]. However, the definition of MRI-negative epilepsy is variable and depends on patients' age, radiologists' expertise, prior knowledge of pathology, use of quantitative morphometric methods to supplement visual analysis, and probably to a lesser degree, on technical specifications of the scanner [2,3]. Children with MRI-negative DRE have different pathological substrates compared to adults. There is a paucity of data about epilepsy surgery outcomes and its determinants in this population [2], such that a meta-analysis found only 93 children with non-lesional epilepsy in studies from 1995 to 2007 [1]. Further, with improving non-invasive localization of seizure-onset zone, surgical candidacy may be extended to children with complex neurophysiology, such as poorly localized ictal-onset on scalp electroencephalography (EEG). We present a single-center series of children with MRI-negative DRE, with a detailed description of their demographic profile, pre-surgical evaluation, surgical procedures, seizure outcomes, and multivariate modeling of predictor variables. We

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believe that this data will contribute toward improved surgical decision making in this population.

2. Methods

2.1. Patient population

Children were identified from an institutional epilepsy surgery electronic database. All children with MRI-negative (defined later) DRE, who underwent resective epilepsy surgery between January 2007 and December 2013 were included. For seizure-free patients a minimum follow-up of one year was required for inclusion. Patients who continued to have seizures for over 3 years after surgery, but subsequently became seizure-free, were not classified as seizure-free for this analysis. Also, for patients who had a repeat resective surgery, the outcomes were classified only with respect to the first surgery.

2.2. Pre-surgical evaluation

The non-invasive pre-surgical evaluation included a detailed history, systematic and neurological examination, testing for genetic causes and/or inborn errors of metabolism, neuropsychological, neurophysiologic, and imaging studies, individualized for all patients by the attending epileptologist. Video-EEG monitoring to capture sufficient number(s) of habitual seizures was carried out. Structural imaging consisted of an epilepsy protocol MRI, described later. Functional imaging comprised of inter-ictal fluoro-deoxyglucose positron emission tomography (FDG-PET), ictal and inter-ictal single photon emission computed tomography (SPECT) and magentoencephalography (MEG) studies. Areas of relative hypo-metabolism were determined by statistical parametric mapping (SPM) of PET data, in addition to visual analysis. Inter-ictal SPECT was digitally subtracted from ictal study and co-registered on MRI (SISCOM) to determine area(s) of relative hyper-perfusion during a seizure. MEG data was obtained with concurrent scalp EEG, and various inter-ictal spikes or ictal onset (if captured) were modeled for source localization using multiple algorithms. Information obtained from different modalities in the non-invasive evaluation was synthesized for each patient individually and reviewed in a multi-disciplinary conference. It was decided, for all except one patient in this series, to proceed for invasive evaluation with implantation of subdural electrodes (this one patient underwent a direct anterior temporal lobectomy with amygdalo-hippocampectomy [ATL-AH]).

After implantation of subdural electrodes under intra-operative electrocorticographic (ECoG) monitoring, all patients had a post-operative head CT scan with 3D reconstruction to verify the location of grids and strips. Again, after a sufficient number of habitual seizures were captured, localization of the central sulcus with somatosensory evoked potentials and functional mapping of motor and/or language cortices with electrical cortical stimulation was performed as clinically indicated. The data was again synthesized and a resection plan was formulated. Additional intra-operative motor mapping was used if proposed resections were adjacent to primary sensorimotor cortex. The details of pre-surgical evaluation at our center have been published earlier [4,5].

2.3. MRI evaluation

MRI was performed at 1.5 T in 4 patients and at 3 T in the remaining ones ($n = 43$). The 1.5 T protocol included: sagittal T1-weighted (5 mm slice thickness, at 6 mm intervals), axial FSE T2-weighted (5 mm slice thickness at 6.5 mm intervals), axial T2 FLAIR (5 mm slice thickness at 6.5 mm intervals), coronal oblique T2 FLAIR (perpendicular to the plane of hippocampus, 4 mm slice thickness at 4 mm intervals), and coronal isotropic 1 mm 3D T1 weighted gradient recalled echo (with 1 mm sagittal and axial multi-planar reformations) sequences. The 3 T protocol included: sagittal isotropic 1 mm 3D T1 weighted gradient recalled echo (with 1 mm axial and coronal multi-planar reformations), axial FSE T2-weighted (3–4 mm slice thickness at 3–4.5 mm intervals), axial T2 FLAIR (4 mm slice thickness at 4.5 mm intervals), coronal oblique T2 FLAIR (perpendicular to plane of hippocampus, 3–4 mm slice thickness at 3–4 mm intervals), and sagittal isotropic 1 mm 3D T2 FLAIR (with 1 mm axial and coronal multi-planar reformations) sequences [6]. MRI was evaluated pre-operatively at the time of multidisciplinary epilepsy conference with access to clinical, EEG, and functional data. Lesional classification was made if the imaging features were strongly suggestive of a potentially epileptogenic lesion which could direct surgical resection. Non-lesional (MRI negative) classification was made if the MRI was completely normal or if there were only non-specific, non-localizing findings that could not direct a surgical plan [6].

2.4. Outcome measures

Seizure outcomes were stratified according to the International League Against Epilepsy (ILAE) outcome classification [7]. ILAE outcome classification is an ordinal scale based on seizure-days/year, with categories defined as complete seizure freedom without auras (I), only auras without other seizures (II), 1–3 seizure-days/year (III), 4 seizure-days/year to a decrease of 50% from pre-treatment seizure frequency (IV), from 50% decrease up to 100% increase (V), and $\geq$100% increase in seizure frequency (VI).

The primary outcome measure was complete seizure freedom (ILAE class 1). A subgroup analysis comparing seizure-free proportions in patients with single seizure semiology and concordant ictal EEG vs. others was also performed. The predictors of seizure freedom including clinical and imaging features, type of surgery, and post-operative histological findings, were also explored. For the purposes of these comparisons, seizure frequency was dichotomized into daily and non-daily seizures. Similarly, children were categorized into those with single seizure semiology vs. those with multiple different seizure types. The concordance of neurophysiological and imaging investigations was based on co-lateralization with the final side of surgery.

2.5. Statistical methods

Data was extracted onto a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA). Proportions, means, and standard deviations were calculated for respective variables. Seizure-free (ILAE class 1) children were compared to those who did not achieve seizure freedom (ILAE class > 1) using Fisher's exact or chi-square tests for categorical variables, and *t*-test for unpaired samples for continuous variables (significant at 2-sided $p \leq 0.05$). All non-invasive pre-surgical variables with $p \leq 0.1$ for univariate analysis were included in a multivariate logistic regression model using forward stepwise variable selection. The regression model was refit with only the selected variables to ensure the largest number of included observations. Odds ratios (OR) and 95% confidence limits (CI) were calculated for statistically significant variables ($p \leq 0.05$). The adequacy of the final model was assessed by examining the area under the receiver-operating-characteristic curve (AUC), and Hosmer–Lemeshow goodness-of-fit test. An identical multivariate analysis was repeated by also including surgical variables. SAS® statistical software version 9.3 (SAS Institute Inc., Cary, NC) was used for statistical analyses.