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Analysis of fractional anisotropy and mean diffusivity in refractory and non-refractory idiopathic generalized epilepsies

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ABSTRACT

Purpose: To compare white matter bundles and fiber tract changes in seizure-free and non-seizure-free idiopathic generalized epilepsy (IGE) patients.

Method: Forty adult patients with IGE underwent a 3 T brain MRI with DTI sequences. According to seizure control status, eighteen patients were classified as refractory (R) if they had presented at least one incapacitating seizure in the previous six months, while on appropriate antiepileptic drug treatment. Twenty two seizure-free patients with adequate seizure control were considered non-refractory (NR). We compared fractional anisotropy (FA) and mean diffusivity (MD) values in sixteen white matter tracts in the R and NR groups, and in twenty healthy subjects.

Results: R and NR groups did not differ in gender, age and education. We found decreased FA in two tracts in the R group (forceps major and right uncinate fasciculus) and approaching statistical significance in two tracts in the NR group (right cingulate gyrus and right uncinate fasciculus) group, as well as increased MD in six tracts in the R group (forceps minor, left thalamic anterior radiation, right inferior longitudinal fasciculus, right longitudinal superior parietal and temporal fasciculi, and right cingulate gyrus) and in five tracts in the NR group (forceps minor, left thalamic anterior radiation, right inferior longitudinal fasciculus, right longitudinal superior parietal and temporal fasciculi), compared to controls. No differences were noted comparing FA and MD values between R and NR groups.

Conclusions: In our patient population, refractory IGE patients on adequate antiepileptic drug treatment did not present more severe white matter tract involvement compared to non-refractory patients.

1. Introduction

Idiopathic generalized epilepsy (IGE) patients usually present normal neuroimaging findings and adequate seizure control if treated with an appropriate antiepileptic drug regimen. Abnormalities in conventional neuroimaging in IGE patients usually represent incidental findings, not related to epilepsy pathophysiology. A significant minority of IGE patients present breakthrough seizures despite appropriate treatment [1]. These patients usually receive higher antiepileptic drug loads.

Advanced neuroimaging techniques, such as DTI (diffusion tensor imaging) tractography have disclosed white matter tracts and bundles abnormalities in IGEs [2]. Thalamic and corpus callosum abnormalities have been described in IGE patients presenting predominately with absence seizures. Frontal region changes have been described in patients with predominant myoclonic seizures [3]. More diffuse white matter changes have also been reported in temporal and occipital regions in IGE patients [4,5].

It is unclear if thalamic and frontal region abnormalities are associated to clinical refractoriness in IGEs

This study evaluated the hypothesis that more widespread white matter fiber tract involvement is associated with clinical refractoriness in IGE patients on adequate antiepileptic drug treatment.

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2. Methods

2.1. Data source

We identified patients with a diagnosis of one IGE syndrome who were followed in the outpatient Epilepsy Clinic of the Neurology Department at Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo. We actively searched patients who were either seizure-free or who had presented at least one incapacitating seizure in the previous six months, despite adequate antiepileptic drug treatment for IGE. Patients were not considered refractory if breakthrough seizures were associated with unexpected sleep deprivation. Seizures were considered incapacitating if they impaired patient's daily life, such as recurrent myoclonic or absence seizures, or occurrence of at least one generalized tonic-clonic seizure.

Patients were searched by manual review of 4252 medical records. We identified 278 patients with a possible diagnosis of IGE. We were able to contact 165 patients by phone call, of which 52 underwent a clinical interview and neurological examination between 2014 and 2016. Forty patients fulfilled IGE criteria, according to ILAE 1989 classification, and were invited to participate in the study.

2.2. Inclusion and exclusion criteria

Patients were included in the study if aged between 18 and 55 years at the time of MRI exam, and if they presented a history of generalized seizures consistent with an IGE diagnosis (generalized tonic clonic, myoclonic and absences), at least one EEG showing generalized epileptiform discharges and a normal neurologic exam.

Patients were not included if they presented an abnormal neurologic exam, a history suggestive of focal seizures or predominant focal EEG abnormalities.

Forty IGE patients were included: twenty two were classified as seizure-free and eighteen patients presented at least one incapacitating seizure in the previous six months, despite regular use of an adequate antiepileptic drug regimen. Patients underwent a clinical evaluation. Medical charts were reviewed regarding EEG reports and neuroimaging findings. Available EEG tracings were reviewed.

Twenty healthy individuals without a history of seizures were included as a control group, using the same inclusion criteria for age, maintaining a similar proportion of men and women as in the patient groups.

2.3. Neuroimaging methods

Participants underwent structural and DTI MRI studies with Philips Intera Achieva 3.0 T using an 8-channel head coil, processed with tract-based spatial statistics (software FSL 5.0 version), yielding absolute fractional anisotropy (FA) and mean diffutivisity (MD) values in sixteen white matter tracts and bundles. Images were processed and represented on TRACULA (tracts constrained by underlying anatomy) DTI format, using the FreeSurfer software package.

DTI sequences were acquired with spin echo (SE) echoplanar diffusion-weighed acquisition, in parallel acquisition (SENSE) in the axial plane, without angulation in 2 mm thickness (70 slices), without interslice interval. *B-value* was 1000 s/mm^2 in 32 non-colinear directions (diffusion gradients). In reference images *b-value* was 0 s/mm^2, TR = 8.500 ms, TE = 61 ms, matrix size = 128 × 128, FOV = 256 × 140 × 256 mm, voxel = 2 × 2 × 2 mm, and acquisition time = 14 min. We acquired the diffusion tensor sequences twice to raise signal-to-noise ratio. Images acquired by the two sequences were merged, and then analyzed as a single acquisition, in 64 directions. Images were pre-processed with standard methods to mitigate image distortions (parasite currents and B0 field inomogeneity). Inidividual diffusion weighted images were recorded with Freesurfer processed anatomical images and common space images (atlas).

We reconstructed volumetric distributions of 18 white matter tracts included in the atlas. Lastly, diffusion measures (FA and MD) were extracted for each reconstructed tract.

2.4. Statistical methods

Groups were compared with variance analysis using ANOVA or Kruskall-Wallis with 2 × 2 post-hoc comparisons (Tukey or Wilcoxon) according to parametric or non-parametric sample features, using the software R (3.1 version). Significance level was established at $p < 0.05$. Statistical computations were performed using the SPSS version 20.0.

3. Results

3.1. Demographics and baseline characteristics

All patients fulfilled IGE syndrome criteria according to the ILAE (International League Against Epilepsy) 1989 classification.

Twelve out of eighteen (66.7%) patients in the R IGE group, fifteen out of twenty two (68.2%) in the NR group, and eleven out of twenty (55%) subjects in the control group were women. Mean age was 32.9 +/− 8.3 (range 20–50 years) in the R group, 32.0 +/-9.0 (range 18–50) in the NR group, and 34.1 +/− 9.8 years (range 19–51 years) in the control group. Mean education was 10.6 +/− 1.4 years in the R group, 11.0 +/− 2.9 years in the NR group, and 11.2 +/− 2.5 years in the control group.

In the refractory group, three patients were diagnosed with childhood absence epilepsy, two patients with juvenile absence epilepsy, eight patients with juvenile myoclonic epilepsy, and five patients with other IGE types. The non-refractory group included two patients with childhood absence epilepsy, twelve with juvenile myoclonic epilepsy, none with juvenile absence epilepsy and eight patients with other IGE types.

3.2. DTI indices comparison

Sixteen white matter tracts were analyzed (Tables 1 and 2). For the refractory group, we found decreased FA in two white matter tracts, and increased MD in five tracts, compared to controls. Comparison between refractory IGE group and controls showed decreased FA values in the forceps major ($p = 0.03$) and the right uncinate fasciculus ($p = 0.02$), and increased MD values in the forceps minor ($p = 0.001$), left thalamic anterior radiation ($p = 0.01$), right inferior longitudinal fasciculus ($p < 0.01$), right longitudinal superior parietal fasciculus ($p = 0.03$), right longitudinal superior temporal fasciculus ($p = 0.01$) and right ($p = 0.03$) cingulate gyrus. In the left cingulate gyrus, the difference approached statistical significance ($p = 0.06$) (Figs. 2 and 4). The non-refractory group of patients showed decreased FA (not reaching statistical significance) in two tracts, and increased MD in five tracts compared to controls. Non-refractory IGE group showed decreased FA values in the right cingulate gyrus (p = 006) and in the right uncinate fasciculus ($p = 0.06$), and increased MD values in the forceps minor ($p < 0.01$), left thalamic anterior radiation ($p < 0.01$), right inferior longitudinal fasciculus ($p < 0.01$), right longitudinal superior parietal fasciculus ($p = 0.03$), and in the right longitudinal superior temporal fasciculus ($p = 0.01$), compared to controls (Figs. 1 and 3). There was no concordance in tracts showing impaired FA and MD parameters for both groups.

We found no statistical differences comparing FA and MD values for the refractory and non-refractory groups.

4. Discussion

The study found decreased FA and increased MD values in both seizure-free and non-seizure-free patients, compared to healthy