ORIGINAL ARTICLE

Diffusion Tensor Imaging Abnormalities in Focal Cortical Dysplasia

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ABSTRACT: ***Purpose:*** Focal cortical dysplasia (FCD) is one of the most common underlying pathologic substrates in patients with medically intractable epilepsy. While magnetic resonance imaging (MRI) evidence of FCD is an important predictor of good surgical outcome, conventional MRI is not sensitive enough to detect all lesions. Previous reports of diffusion tensor imaging (DTI) abnormalities in FCD suggest the potential of DTI in the detection of FCD. The purpose of this study was to study subcortical white matter underlying small lesions of FCD using DTI. ***Methods:*** Five patients with medically intractable epilepsy and FCD were investigated. Diffusion tensor imaging images were acquired (20 contiguous 3mm thick axial slices) with maps of fractional anisotropy (FA), trace apparent diffusion coefficient (trace/3 ADC), and principal eigenvalues (ADC parallel and ADC perpendicular to white matter tracts) being calculated for each slice. Region of interest analysis was used to compare subcortical white matter ipsilateral and contralateral to the lesion. ***Results:*** Three subjects with FCD associated with underlying white matter hyperintensities on T2 weighted MRI were observed to have increased trace/3 ADC, reduced fractional anisotropy and increased perpendicular water diffusivity which was greater than the relative increase in the parallel diffusivity. No DTI abnormalities were identified in two patients with FCD without white matter hyperintensities on conventional T2-weighted MRI. ***Conclusions:*** While DTI abnormalities in FCD with obvious white matter involvement are consistent with micro-structural degradation of the underlying subcortical white matter, DTI changes were not identified in FCD lesions with normal appearing white matter.

RÉSUMÉ: Anomalies de l'imagerie par résonance magnétique du tenseur de diffusion dans les dysplasies corticales focales. ***But:*** La dysplasie corticale focale (DCF) est une des pathologies sous-jacentes les plus fréquentes chez les patients présentant une épilepsie réfractaire au traitement médical. Bien que des manifestations de DCF à l'IRM soient un élément important prédisant un bon résultat chirurgical, l'IRM conventionnelle n'est pas assez sensible pour détecter toutes les lésions. Selon certaines publications, l'imagerie par résonance magnétique du tenseur de diffusion (ITD) pourrait être utile pour la détection de la DCF. Le but de cette étude était d'étudier la substance blanche sous-corticale de petites lésions de DCF au moyen de l'ITD. ***Méthodes:*** Nous avons évalué cinq patients atteints d'épilepsie réfractaire au traitement médical et de DCF au moyen de l'ITD (vingt coupes axiales contiguës de 3 mm d'épaisseur) avec cartographie de l'anisotropie fractionnaire (AF), du coefficient apparent de diffusion (trace/3 ADC) et calcul des valeurs eigen principales (ADC parallèle et perpendiculaire aux faisceaux de la substance blanche) pour chaque coupe. La substance blanche sous-corticale homolatérale et controlatérale des régions d'intérêt a été comparée. ***Résultats:*** Chez trois sujets atteints de DCF associée à des zones de substance blanche hyperintenses à l'IRM pondérée en T2 on a observé une augmentation de trace/3 ADC, une diminution de l'AF et une augmentation de la diffusivité aqueuse perpendiculaire qui était plus grande que l'augmentation relative de la diffusivité parallèle. Aucune anomalie ITD n'a été identifiée chez deux patients atteints de DCF sans zones d'hyperintensité au niveau de la substance blanche à l'IRM conventionnelle pondérée en T2. ***Conclusions:*** Bien que des anomalies de l'ITD chez les patients atteints de DCF ayant une atteinte évidente de la substance blanche soient en faveur d'une altération micro-structurale de la substance blanche sous-corticale sous-jacente, aucun changement n'a été identifié à l'ITD dans les lésions de DCF où la substance blanche semble normale.

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Focal cortical dysplasia (FCD) was first described in 1971 and has subsequently been demonstrated to be one of the most important causes of medically intractable epilepsy.[1,2] Focal cortical dysplasia is associated with: disruption of cortical lamination with poorly differentiated glial cell elements, heterotopic neurons, atypical cells and disorganization of subcortical white matter.[1,3] Macroscopically, FCD lesions are associated with thickening of the cortical grey matter and blurring of the grey-white junction, which, along with increased T2 signal, can be detected with magnetic resonance imaging (MRI).[1,4,5] In many cases, however, these findings can be difficult to detect with conventional imaging techniques (such as T1 and T2 weighted imaging).[5,6] As the surgical outcome in medically intractable patients is dramatically improved in subjects in whom a lesion is identified on MRI,[7] there is a need to continue to improve the sensitivity of MRI in the detection of FCD.

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Diffusion Tensor Imaging (DTI) is an exciting new MRI technique that can be used to indirectly evaluate the integrity of the axonal micro-environment by measuring the diffusion of water and its directionality in three dimensions. Given the parallel organization of nerve fibers, diffusion of water is normally hindered by membranes in the direction perpendicular to their principal axis (i.e. anisotropic, parallel diffusion is faster than perpendicular diffusion), whereas in a medium that lacks barriers to water movement, such as cerebral spinal fluid (CSF), diffusion of water is the same in all directions (i.e. isotropic).[8-10] Anisotropy can be quantified in each voxel using the index of Fractional Anisotropy (FA) with values ranging from zero (isotropic diffusion) to one (highly anisotropic diffusion).[11] Other diffusion imaging derived parameters include the trace Apparent Diffusion Coefficient (trace/3 ADC) which yields the mean bulk mobility of the water and the eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) that correspond to the directional apparent diffusion coefficients either along the fiber tracts (ADC parallel = $\lambda1$) or perpendicular to them (ADC perpendicular = $(\lambda2 + \lambda3)/2$). In normal fiber tracts water diffusion is anisotropic (i.e. high FA), whereas in degenerated tracts the FA drops substantially.[12-14] Reduced FA values reflect a disproportionate increase in ADC perpendicular as compared to ADC parallel. Reduced FA is presumed to reflect one of three basic pathological mechanisms: 1) degradation of axonal membranes and myelin (i.e. Wallerian degeneration),[12-14] 2) abnormalities of myelin with sparing of the axons (i.e. demyelination or dysmyelination)[15,16] or 3) reduced density of myelinated axons (i.e. maldevelopment).[17] Further, a recent study correlating DTI findings with histology in a mouse model of retinal ischemia has demonstrated that a reduction of ADC parallel correlated with axonal degeneration while an increase in ADC perpendicular correlated with myelin breakdown.[18] These observations suggest that analysis of eigenvalues can provide further insight into the underlying pathological process responsible for changes in FA.

Reduced FA has been reported in the subcortical white matter underlying cortical abnormalities in patients with malformations of cortical development,[19] as well as in FCD.[20-22] Of interest, reduced FA has also been reported to extend beyond the extent of the obvious cortical abnormality in some patients.[19,22] Abnormalities of bulk diffusion (elevation in trace/3 ADC) have been less consistent, being observed in ten of 22 patients with malformations of cortical development[19] and one of three subjects with FCD.[20] Using diffusion tensor tractography, Lee et al.[21] have recently reported a subjective decrease in subcortical fibres underlying the lesion in 12 patients with FCD. Specific results on the directional apparent diffusion coefficients (i.e. ADC parallel and ADC perpendicular) have not, however, been previously reported.

The objective of this study was to assess whether DTI could detect white matter changes underlying FCD by studying a series of patients with FCD both with and without obvious underlying white matter pathology. Furthermore, the DTI parameters (FA, trace/3 ADC, ADC parallel and ADC perpendicular) were used to gain further insight into the nature of the underlying white matter pathology.

Subjects and Methods

Approval of the research protocol was obtained from the University of Alberta Health Research Ethics Board and informed consent was obtained from all participants.

Subjects: A series of five patients with medically intractable epilepsy and pathologically documented FCD or typical MRI features of FCD[4,5] were included in the study. All patients had previously undergone clinical MRIs using our standard epilepsy protocol including: high resolution volumetric T1, axial and coronal T2 and axial Fluid Attenuation Inversion Recovery (FLAIR). Patient one is a 14-year-old female with left anterior frontal translaminar dysplasia (i.e. blurring of the grey-white junction and hyperintense T2 signal extending from the lateral ventricle to the cortical surface) (Figure 1). Patient two is a 17-year-old female with a right frontal translaminar dysplasia (Figure 1). Patient three is a 28-year-old male with a left occipital-parietal lesion associated with thickened cortex and hyperintense T2 signal in the subcortical white matter (Figure 1). Patient four is a 28-year-old female with an active right frontal interictal EEG abnormality and a focal region of blurring of the grey-white matter junction in the right frontal convexity without evidence of signal abnormality in the subcortical white matter. The dysplastic lesion was only apparent on curvilinear reconstruction of volumetric T1 weighted MRI. Patient five is a 25 year old female with an active right frontal ictal and interictal EEG abnormality and no apparent lesion on high resolution MRI including curvilinear reconstruction of T1 weighted MRI. Both patients four and five underwent invasive electroencephalogram (EEG) monitoring and focal cortical resection with pathological confirmation of microscopic FCD in both cases.

Imaging Protocol: Diffusion tensor images were obtained on a 1.5T Siemens Sonata scanner using CSF-suppressed, single-shot spin-echo diffusion echo planar imaging (EPI): (repetition time (TR) = 7600 ms, echo time (TE) = 88 ms, inversion time (TI) = 2200 ms, 8 averages, field of view (FOV) = 220 mm, twenty 3 mm thick contiguous axial slices with a 1 mm gap, 96 x 128 matrix zero filled to 256 x 256, acquisition voxel resolution of 2.3 x 1.7 x 3 mm^3, scan time 8 min. The diffusion tensor was acquired with diffusion gradients along six non-collinear directions (b=1000 s/mm^2) and one without diffusion weighting (b=0 s/mm^2). Maps of fractional anisotropy (FA), trace/3 ADC (the mean of the three principal eigenvalues), and principal eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) were calculated for each slice using MRVision software (MRVision, Winchester, MA). Apparent Diffusion Coefficient parallel to the fibre tracts is given by the largest eigenvalues (ADC parallel = $\lambda1$) and ADC perpendicular by the mean of the two smaller eigenvalues (ADC perpendicular = $(\lambda2 + \lambda3)/2$).

Analysis: Regions-of-interest (ROI) were identified within visible hyper-intensities on the CSF-suppressed non-diffusion-weighted (i.e. b=0 s/mm^2) images and transferred to the diffusion parametric maps for patients one (three slices), patient two (three slices) and patient three (ten slices). The ROI's were outlined underlying the subdural grid ictal focus which corresponded with the right frontal cortical grey matter abnormality for patient four (three slices) and underlying the subdural grid ictal epileptic focus in two slices for patient five. Curvilinear reconstruction of MRI with grid in place was used to correlate the location of active subdural grid electrode contacts with the underlying cortical anatomy for both patients four and five (Figure 2). The ROI's were confined to the subcortical white matter. For each

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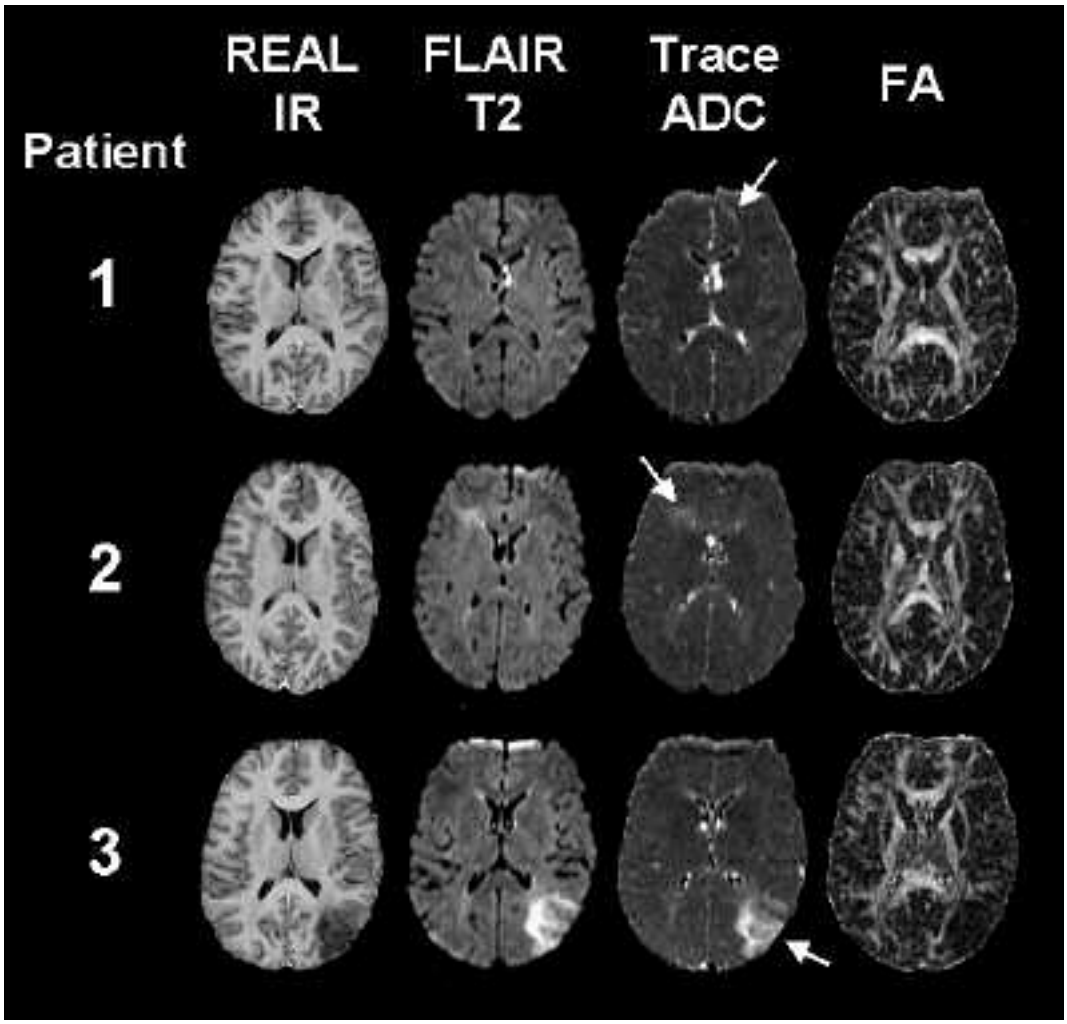

Figure 1: Imaging findings in subjects with white matter changes. *Axial T1 weighted (acquired using a real constructed inversion recovery (IR) sequence), FLAIR (T2), mean apparent diffusion coefficient (trace ADC) and fractional anisotropy (FA) maps for representative single slices of the three patients with high T2 signal abnormalities in the subcortical white matter. Patients one and two have typical translaminar FCD (patient one- left frontal, patient two- right frontal) with thickened cortical grey matter, blurring of the grey-white junction and high T2 signal abnormalities of the white matter that extends from the cortex to the lateral ventricle. Patient three has a large left parietal-occipital lesion with thickened gyri and extensive subcortical white matter T2 hyperintensity. Note the elevated mean diffusivity (i.e. given by trace ADC) and the reduced structural orientation (i.e. given by fractional anisotropy, FA) of the underlying subcortical white matter.*

subject, mean values (for T2 signal intensity, trace/3 ADC and FA) were calculated both ipsilateral and contralateral to the lesion. For the contralateral "normal" side, the mean and standard deviation of all five patients was determined and compared to the ipsilateral values for each patient. Individual patient results were considered abnormal if they fell outside of two standard deviations of the contralateral values. Similar analysis of ADC parallel and ADC perpendicular were performed, however, analysis was limited to patients who demonstrated abnormalities of FA. The contralateral anisotropy values (FA values between 0.41 and 0.54) were similar to those measured with CSF suppression in the subcortical white matter of the gyri in healthy controls.[23]

Results

For patients one, two and three (all three who had subcortical T2 signal abnormality), the white matter hyperintensities on the non-diffusion-weighted FLAIR images (i.e. T2 weighted) was greater than two standard deviations of the contralateral values. These three patients all had increased mean diffusivity, given by trace/3 ADC (> 2SD) and reduced directionality of water diffusion, FA (< 2SD), ipsilateral to the lesion relative to the contralateral subcortical white matter (Figure 3). The ADC parallel was increased in two of three patients (> 2SD) and ADC perpendicular in all three patients (> 2SD) (Figure 3). The two patients without subcortical white matter T2 weighted hyperintensities (patients four and five) had no asymmetry in: T2 signal, trace/3 ADC or FA for the ipsilateral subcortical white

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matter (Figure 3), with findings being similar to control subjects.[23]

Discussion

Although there is a considerable literature regarding diffusion changes in malformations of cortical development, the sensitivity of the technique in detecting small FCD lesions remains unclear. While Eriksson et al. found reduced FA in the majority of their patients with malformations of cortical development, most of the subjects studied had large regional abnormalities and only one of 22 patients studied could be classified as FCD.[19] Dumas de la Roque et al[22] do not state specifically whether their six subjects with cortical malformations had white matter abnormalities, however, the one illustrated case has typical MRI findings of a translaminar cortical dysplasia (i.e. with obvious signal abnormality in the subcortical white matter). Wieshmann et al[20] report reduced FA in three patients with FCD all of whom had signal change in the subcortical white matter (i.e. similar to our patients 1-3). The largest study of FCD to date by Lee et al[21] includes 12 subjects (five of which had white matter abnormalities and seven that did not). While the authours report a significant reduction of FA in the underlying subcortical white matter overall, they do not comment on whether reduced FA was observed in both patients with and without white matter hyperintensities on T2 weighted imaging.[21]

Our findings of reduced FA in patients with FCD and underlying white matter signal change (patients 1-3) is consistent with the findings of Wieshmann et al.[20] While Wieshmann et al[20] report elevated trace ADC in one of three subjects,[20] all three of our patients demonstrated trace ADC greater than two standard deviations of the contralateral white matter. Analysis of ADC parallel and ADC perpendicular allows further understanding of the observed reduction in FA values. Decreased FA (patients 1-3) resulted from a disproportionate increase in ADC perpendicular as compared to ADC parallel (Figure 3). This observation suggests that decreased myelination is the primary underlying pathological process responsible for the observed FA changes as opposed to axonal degeneration where reduced parallel diffusion would be expected.[16,18] Of interest, this observation is consistent with histological demonstration of hypomyelination observed in surgical specimens of focal translaminar cortical dysplasia.[24]

We were, however, unable to detect DTI changes underlying lesions in the two patients in our study with pathologically confirmed FCD who did not have subcortical white matter hyperintensities on T2 weighted MRI. Several possible

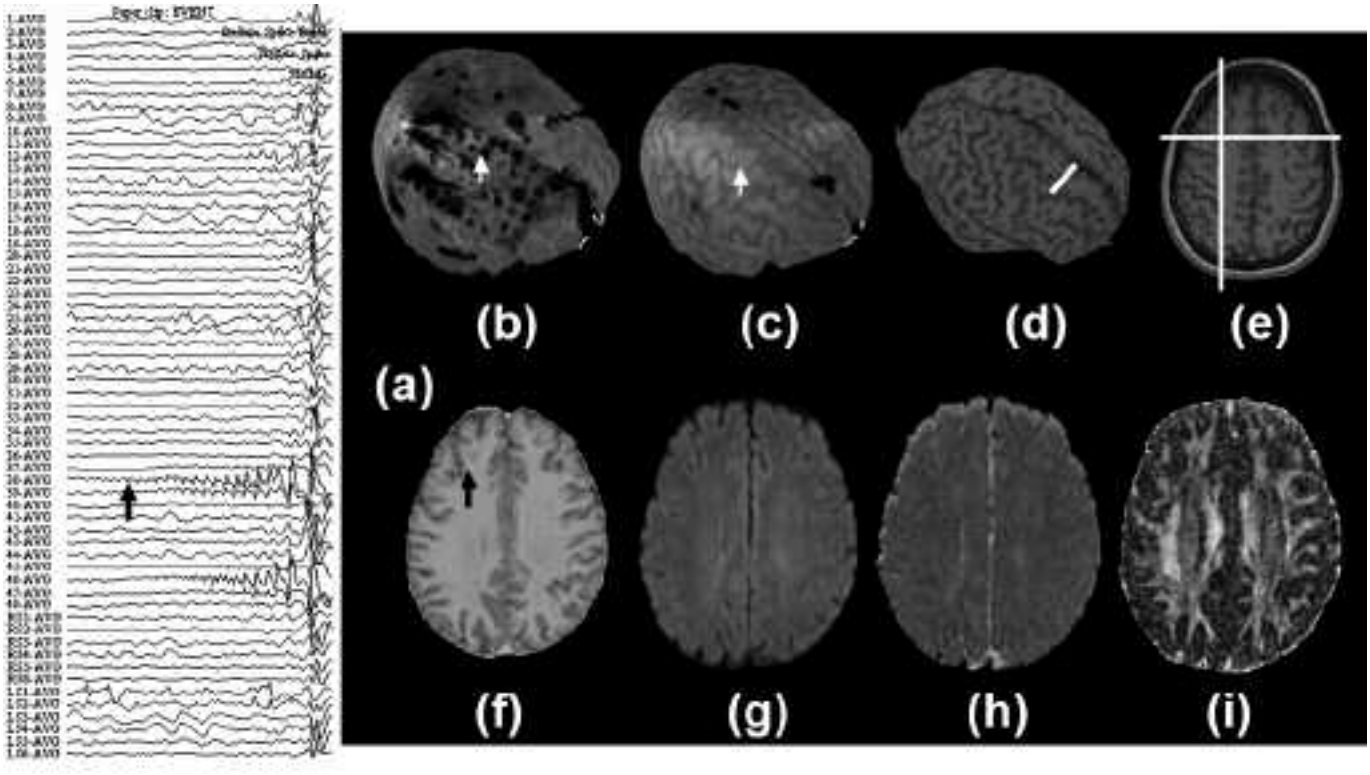

Figure 2: Region of interest placement in patients without obvious white matter abnormalities. *Intracranial electroencephalogram (EEG) and MRI data for patient four. (a) Subdural grid recording demonstrating focal ictal EEG onset at electrode contact 38 (arrow) with subsequent spread to surrounding contacts 39 and 46. (b, c) Curvilinear reformatted volumetric T2 weighted MRI with subdural grid in place (b) superficial slice demonstrating location of grid and (c) deeper slice demonstrates underlying cortical anatomy (arrow indicates the location of contact 38). (d,e) Volumetric T1 weighted MRI (d) curvilinear and (e) axial slice. (d) The marker indicates trajectory line from corresponding location on axial slice. Curvilinear reformatted T1 weighted and T2 weighted (with grid in place) data was used to determine the region of interest on axial MRIs. (f) Axial T1, (g) FLAIR, (h) trace ADC and (i) FA maps for patient four. (f) The arrow indicates subcortical white matter directly underlying the gyral abnormality. No obvious abnormalities are observed in the underlying subcortical white matter on FLAIR, trace ADC or FA for this patient.*

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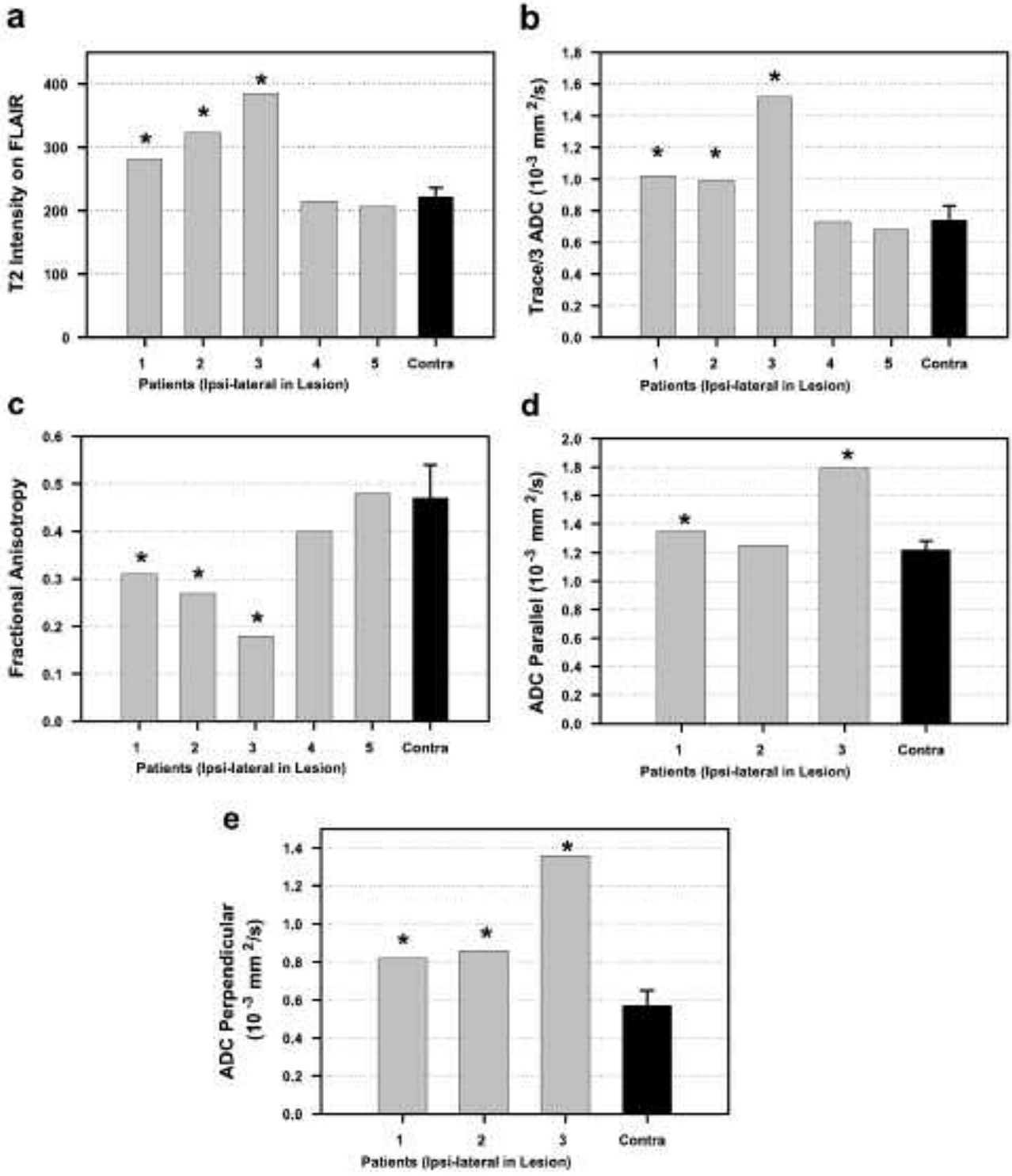

Figure 3: Comparison of diffusion parameters ipsilateral and contralateral to dysplasia. *(a) T2 signal intensity; (b) mean diffusivity, trace/3 ADC; (c) fractional anisotropy, FA; (d) parallel diffusivity, λ1; and (e) perpendicular diffusivity, (λ2 +λ3)/2 of the subcortical white matter ipsilateral to the dysplastic lesion as compared to the mean contralateral value of all patients (* reflects values that are outside of two standard deviations of the contralateral hemisphere). The ADC parallel and ADC perpendicular are only given in subjects that demonstrated abnormalities in FA. All patients with T2 weighted signal abnormality of the subcortical white matter (patients 1-3), were observed to have elevated bulk diffusion (trace/3 ADC) and reduced fractional anisotropy (FA) while no differences in trace/3 ADC or FA were observed for the patients without white matter T2 signal change (patients 4,5). The ADC perpendicular was elevated in all three patients with reduced FA (ipsilateral/mean contralateral: patient 1- 1.44, patient 2- 1.50, patient 3- 2.38) while ADC parallel was elevated in two of three patients (ipsilateral/mean contralateral: patient 1- 1.11, patient 2- 1.02, patient 3- 1.46).*

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explanations exist for our inability to detect DTI abnormalities in these two patients. The absence of diffusion abnormalities may reflect limitations in the spatial resolution of our DTI sequence and it is possible that DTI obtained with higher angular resolution (i.e. more diffusion-sensitizing gradient directions), better spatial resolution, and larger static magnetic field could allow the detection of subtle changes that were undetected with our current protocol. The absence of DTI changes in these patients could also reflect differences in the underlying pathology of the lesions. Disorganization of the subcortical white matter would be expected even in small FCD lesions.[1] It is possible that hypomyelination (which has been demonstrated in translaminar dysplasia[24] and which we suspect was responsible for the diffusion changes in patients 1-3) is either absent or not severe enough to affect water diffusion properties in the two patients without white matter signal change on T2 weighted imaging.

While our observation of DTI abnormalities that were concordant with conventional MRI findings in patients with focal translaminar dysplasia is encouraging and suggests the possibility that DTI may be a useful tool in the characterization of FCD, further development is required to determine the sensitivity of the technique in the detection of small FCD lesions without subcortical white matter signal abnormalities.

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