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SHORT COMMUNICATION

Advanced diffusion imaging sequences could aid assessing patients with focal cortical dysplasia and epilepsy☆

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Summary Malformations of cortical development (MCD), particularly focal cortical dysplasia (FCD), are a common cause of refractory epilepsy but are often invisible on structural imaging. NODDI (neurite orientation dispersion and density imaging) is an advanced diffusion imaging technique that provides additional information on tissue microstructure, including intracellular volume fraction (ICVF), a marker of neurite density.

We applied this technique in 5 patients with suspected dysplasia to show that the additional parameters are compatible with the underlying disrupted tissue microstructure and could assist in the identification of the affected area.

The consistent finding was reduced ICVF in the area of dysplasia. In one patient, an area of reduced ICVF and increased fibre dispersion was identified that was not originally seen on the

Abbreviations: CNR, contrast-to-noise ratio; CSF, cerebrospinal fluid; FA, fractional anisotropy; FCD, focal cortical dysplasia; FLAIR, fluid-attenuated inversion recovery; ICVF, intracellular volume fraction; ITG, inferior temporal gyrus; MCD, malformations of cortical development; MD, mean diffusivity; MFG, middle frontal gyrus; MRI, magnetic resonance imaging; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction.

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structural imaging. The focal reduction in ICVF on imaging is compatible with previous iontophoretic data in surgical specimens, was more conspicuous than on other clinical or diffusion images (supported by an increased contrast-to-noise ratio) and more localised than on previous DTI studies.
NODDI may therefore assist the clinical identification and localisation of FCD in patients with epilepsy. Future studies will assess this technique in a larger cohort including MRI negative patients.

Introduction

A third of patients with focal epilepsy are refractory to medical treatment. Identification of the epileptogenic zone is critical in planning surgical treatment but up to 20—30% of patients have normal structural magnetic resonance imaging (MRI) scans (Duncan, 2010). Drug-resistant epilepsy is associated with malformations of cortical development (MCD) in 15—20% of adult patients and over 50% of paediatric patients.

The most common type, focal cortical dysplasia (FCD), is frequently not detected on structural MRI and up to 42% of MRI-negative patients undergoing surgery have FCD (Chapman et al., 2005). FCD is characterised by disrupted laminar architecture and columnar organisation and abnormal cells, including dysmorphic neurons and balloon cells (Blumcke et al., 2011). Studies on neocortical tissue from surgically resected temporal lobe specimens with FCD demonstrate altered diffusion parameters in the extracellular space and, in type II, a reduced intracellular volume fraction (ICVF) (Vargova et al., 2011).

Typical neuroimaging features of FCD including cortical thickening and blurring of the grey-white matter boundary on T1-weighted images and cortical and subcortical signal hyperintensities on T2-weighted images are not always present (Barkovich and Kuzniecky, 1996). Diffusion tensor imaging (DTI) demonstrates abnormal diffusion indices in underlying white matter, including reduced fractional anisotropy (FA) and increased mean diffusivity (MD). However these are non-specific, extend beyond the area of abnormality (Eriksson et al., 2001) and cannot evaluate dysplastic grey matter due to the low FA and signal contamination by cerebrospinal fluid (CSF).

The assumption inherent in DTI that each voxel contains a single tissue compartment with Gaussian diffusion is increasingly recognised as inadequate. Multi-compartment models more accurately reflect the diffusion MR signal by modelling several tissue compartments and distinguishing restricted non-Gaussian diffusion (intracellular) from hindered Gaussian diffusion (extracellular space) but the lengthy scans required are often clinically unfeasible (Panagiotaki et al., 2012).

The NODDI (neurite orientation dispersion and density imaging) model includes three compartments for each voxel — intracellular, extracellular and CSF — and provides additional estimates of tissue microstructure in both grey and white matter. It distinguishes two key variables contributing to changes in FA — neurite density (ICVF) and fibre orientation dispersion — with a clinically feasible scan protocol of 20 min (Zhang et al., 2012) so could potentially assist the identification and understanding of FCD.

We describe a preliminary study in which the NODDI model is applied for the first time in a clinical population of patients with epilepsy and suspected dysplasia on conventional imaging. The aims are to determine firstly whether the parameters estimates are compatible with the underlying disrupted tissue microstructure and secondly whether they potentially provide useful additional clinical information for localising the abnormality. This proof-of-concept study lays the foundation for future larger studies.

Methods

Five consecutive patients with previous structural imaging findings compatible with FCD (4 patients) or tuberous sclerosis (TS, 1 patient) attending for further imaging as part of pre-surgical assessment were invited to undergo an additional NODDI protocol optimised for a 3T GE Signa HDx scanner (Alexander, 2008). The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee, and informed written consent was obtained from all subjects. Patient demographics and clinical data are listed in Table 1.

The protocol consisted of two high angular resolution diffusion imaging shells (single-shot EPI, 50 mm × 2.5 mm axial

Table 1 Demographic and clinical characteristics of patients.

Patient	Age/gender	Age at seizure onset (years)	Structural MRI report	Video EEG localisation
1	21/M	2	Right MFG resection with residual FCD	Right frontocentral
2	27/M	8	Left ITG FCD	Left anterior temporal
3	62/M	17	Left ITG FCD/dysplasia	Left anterior temporal
4	31/F	6	Cortical tubers, largest in right ITG	Right anterior temporal
5	28/M	10	Normal, then L MFG MCD (FCD or polymicrogyria)	Left frontocentral