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The role of the corpus callosum in seizure spread: MRI lesion mapping in oligodendrogliomas

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Summary
Background: Some patients with oligodendrogliomas have generalized tonic—clonic seizures (GTCS) while others have only partial seizures (PS). We investigated the relationship between tumour localization and seizure generalization using quantitative lesion mapping on magnetic resonance images.
Methods: Twenty one patients with histologically proven oligodendrogliomas and GTCS ($n = 11$) or PS ($n = 10$) were studied. Data were acquired on a 3 Tesla MRI System. We performed lesion mapping techniques to compare the spatial distribution of oligodendrogliomas between patient groups, and quantitatively determined the extent to which lesions intersected each probabilistic regions-of-interest, including the cerebral lobes, thalamus, striatum, and genu of the corpus callosum.
Results: In patients experiencing GTCS, the greatest lesion load was observed in mesial frontal regions, including cortex connected to the genu. In contrast, the greatest lesion load in patients experiencing PS was observed more caudo-laterally in orbitofrontal and temporal lobes, but typically sparing cortex connected to the genu. The number of lesion intersections with genu region of interest was significantly greater in patients experiencing GTCS relative to patients with PS ($p = 0.03$). There were no significant differences between patient groups with

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respect to lesion intersection with the individual cerebral lobes, thalamus and striatum, or with respect to overall oligodendroglioma size.
Conclusion: Our data suggest that the genu of the corpus callosum may be a major pathway for seizure generalization in patients with oligodendrogliomas.

Introduction

Epileptiform activity and clinically manifest seizures occur when a population of cells in the grey matter begins to fire excessively (Dodson, 2004). It is generally accepted that such pathological synchronized activity results from an imbalance of excitation and inhibition in cortical circuits at multiple levels. Seizure semiology and severity is determined by the spread of this synchronized activity to other parts of the brain. Seizure spread is very difficult to study because large parts of the brain are inaccessible for surface EEG. The study of seizure spread has been largely limited to the small minority of patients who have been investigated with invasive EEG as part of the pre-surgical work up for epilepsy surgery.

Oligodendrogliomas are intrinsic brain tumours that frequently present with epileptic seizures. About 70% of patients present with seizures (Ketz, 1974). Seizures can be the only manifestation of low grade gliomas including oligodendrogliomas (Morris et al., 1993). It is generally accepted that white matter, infratentorial and basal tumours are less epileptogenic then those in the cortex of the cerebral hemispheres. However, the types of seizures associated with brain supratentorial tumours have often been analyzed and widely divergent results have been obtained (Ketz, 1974). Some patients with oligodendrogliomas have only partial seizures, which may be fleeting sensations, resulting in a delay of the diagnosis. Other patients experience solely or predominantly secondary generalized seizures, often with an absence of, or very brief, aura. In the present study, we studied the relationship between seizure semiology and tumour location in a cohort of patients with oligodendrogliomas. In particular, using lesion-mapping techniques applied to MRI scans, we specifically explored the association between seizure type (generalized tonic clonic seizures (GTCS) or partial seizures (PS)) with tumour location.

Methods

Participants

The study was performed as part of an audit on oligodendrogliomas and was approved by the appropriate hospital review panel. We obtained a list of 151 patients with histological proven oligodendrogliomas from a neuropathological database. In 46 patients an MRI volume scan was available and we randomly selected 22 patients, one of whom had to be excluded because of artefacts on volume scans leaving eleven patients with GTCS and ten with PS. The patients had attended the Walton Centre over a timespan of 10 years. The average duration to surgery was for *gtcs 30 month (Standard deviation (SD) 40.5 month) and for PS 25.5 month (SD 39.4 month)*. The clinical data are shown in Table 1.

MRI analysis

MRI data were acquired on a 3 Tesla MRI System (Philips Achieva). Quantitative image analysis studies were performed on 3D T1-weighted images acquired axially (TR = 9.76, TE = 4.59, Flip Angle = 8, voxel size = 1 mm × 1 mm × 1 mm, image dimensions = 182 × 218 × 182). We performed a lesion-mapping technique to determine the topological distribution of oligodendrogliomas in standard space based on previously published methods (Rorden et al., 2007), with a goal of determining whether lesion load in a particular brain region was related to GTCS. Initially, all images were realigned into the same anterior commissure—posterior commissure orientation using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Realigned images were imported into MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron) for manual delineation of lesions in native (subject-specific) space by KM, who was blinded to the clinical data. Oligodendrogliomas were delineated primarily in the acquired axial plane, with simultaneous reference to coronal and sagittal sections. Segmented lesions were saved as a separate file and binarised. We used FSL (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library) tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) for the spatial transformation of images and lesion segmentations to standard space, as previously done for lesion mapping. In particular, both affine (FLIRT; FSL Linear Image Registration Tool) and non-linear (FNIRT; FSL Nonlinear Image Registration Tool) transformations were used to register each image to the Montreal Neurological Institute (MNI) 152 coordinate system, which is a T1-weighted atlas constructed from 152 images in standard space (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6). The non-linear warps used to register images to the standard template were applied to the corresponding segmented binarised lesions, which transformed lesions into standard non-linear (MNI) space. Fig. 1 shows examples of lesion delineation and spatial normalization in two exemplar cases. FSL utility tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils) were used to determine the voxel-wise topology of lesions common to patients with GTCS and PS separately by concatenating all spatially normalised lesions into an individual image file per group (using 'fslmerge') and determining the number of times a voxel was intersected by a lesion (using 'fslmaths'). The result was a single image file that was colour-coded according to the number of times each voxel was lesioned for each group, and which was superimposed onto the MNI template MR image for neuroanatomical reference.

Lesion mapping provided an opportunity to visualise the differences in lesion load between the two patient groups. In order to test our hypotheses quantitatively, we determined whether each spatially normalized lesion intersected, and