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Proton magnetic resonance spectroscopy of malformations of cortical development causing epilepsy

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Summary
Purpose: To use proton magnetic resonance spectroscopy (MRS) to measure concentrations of gamma-aminobutyric acid (GABA) and glutamate plus glutamine (GLX) in adult patients with refractory epilepsy associated with malformations of cortical development (MCD).
Methods: We used MRS to measure *N*-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr) and choline containing compounds (Cho), as well as GLX, and GABA. Fifteen patients with epilepsy attributable to MCD and 15 healthy controls were studied. Nine of the MCD group had heterotopia and six had polymicrogyria. Quantitative short echo time MRS [echo time (TE) = 30 ms, repetition time (TR) = 3000 ms] was performed in the MRI evident MCD and in the occipital lobes of the control group and the concentrations of NAA, Cr, Cho, and GLX were measured. GABA plus homocarnosine (GABA+) was measured in the same regions using a double quantum filter.
Results: The dominant abnormalities in the patient group were elevation of Cho and GLX and reduction in NAAt compared to the control group. The ratios GLX/NAAt and GABA+/Cr were also increased in the patient group whilst the ratio NAAt/Cr was decreased. NAAt was significantly lower in polymicrogyria than heterotopia.
Conclusions: Large cortical malformations had abnormal levels of both GLX and GABA+/Cr. Low NAAt and high Cho were also observed. These results indicate that MCD show spectroscopic features of primitive tissue and abnormal metabolism of both inhibitory and excitatory neurotransmitters.

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Introduction

Malformations of cortical development (MCD) are an important cause of refractory focal epilepsy. MCD include a heterogeneous range of conditions that arise at different points along the process of normal cortical development, which have characteristic histopathological features and recognisable appearance on MRI. Microscopic structure of these MCD sub-types can range from heterotopic aggregates of relatively normal neurons to abnormalities of cortical lamination or neuronal differentiation. Invasive EEG studies have demonstrated that MCD are intrinsically epileptogenic (Kothare et al., 1998; Mattia et al., 1995; Palmini et al., 1995) or that surrounding normal appearing tissue is epileptogenic (Jacobs et al., 1999).

Proton magnetic resonance spectroscopy (MRS) is a sensitive measure of neuronal loss or dysfunction (Cendes et al., 1997; Tasch et al., 1999; Urenjak et al., 1992) or neuronal maturation (Kreis et al., 2002; Tkac et al., 2003), and recent MRS studies have reported the reliable quantification of metabolites relevant to the study of epilepsy (McLean et al., 2000; McLean et al., 2002; Petroff et al., 2000). Most MRS studies in subjects with MCD have used long echo times (TE), and reported only the ratios of the main visible metabolites, *N*-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr), and choline containing compounds (Cho) (Kuzniecky et al., 1997; Li et al., 1998; Marsh et al., 1996; Mueller et al., 2005; Simone et al., 1999; Widjaja et al., 2003). These studies have typically shown reduction in NAA/Cr and NAA/Cho in the region of focal cortical dysplasia whilst heterotopia and polymicrogyria may have normal or reduced NAA/Cr (Kuzniecky et al., 1997; Li et al., 1998; Marsh et al., 1996; Widjaja et al., 2003). There is evidence for metabolic heterogeneity within the visible lesions as well as within normal appearing surrounding tissue (Mueller et al., 2005). In a quantitative multi voxel MRS study of MCD with correction for tissue composition we found abnormal metabolite concentrations within MCD, within peri-lesional tissue and also in contralateral normal appearing tissue (Woermann et al., 2001).

Elevation of glutamate is a feature of epileptic tissue (Petroff et al., 1995) and elevations in GLX have been observed in the frontal lobes in subjects with idiopathic generalised epilepsy (IGE) (Simister et al., 2003b) and in the temporal lobe in temporal lobe epilepsy (Woermann et al., 1999).

The role of GABA in the developing brain and in epileptic tissue is the subject of much current research. Reduction in GABA inhibition may cause seizures (Olsen and Avoli, 1997) and several potent anti-epileptic drugs (AED) enhance GABA function. However, in immature or epileptic tissue, activation of GABAergic synapses may be excitatory rather than inhibitory (Ben Ari, 2002; Ben Ari and Holmes, 2005). Although in vivo identification of GABA via MRS is difficult due to overlapping metabolite peaks, methods such as spectral editing have been developed to separate the GABA signal to allow quantification (Henry et al., 2001; Kuzniecky et al., 2002; Mescher et al., 1998; Mueller et al., 2001; Petroff et al., 1996, 1999a,b, 2000, 2001). We have reported the reliable measurement of GABA+ using a double quantum filter (DQF) (Simister et al., 2003b). As with spectral editing methods the resulting ''GABA'' peak includes homocarnosine, glutathione and some macromolecule signal so we designate our measures as GABA+. Homocarnosine is a dipeptide of GABA and histidine. Its localization appears to be the cytosol of a sub-group of GABAergic neurons and it may act as a GABA reservoir (Henry and Theodore, 2001). Measurements in subjects with epilepsy without MRI evidence of MCD have shown low (Petroff et al., 1996, 2000, 2001) or unchanged GABA+ levels (Simister et al., 2003b,a) compared to a control population. Levels of GABA+ (Petroff et al., 1996) and homocarnosine (Petroff et al., 2000, 2001) increased with improved seizure control or following the administration of vigabatrin, topiramate (TPM) or gabapentin (GBP) (Kuzniecky et al., 2002; Mueller et al., 2001; Petroff et al., 2000). In contrast, GABA concentrations were elevated in ex vivo measurements of focal cortical dysplasia (Aasly et al., 1999). Animal models of MCD have shown increased GABAergic function associated with impaired GABA transporter function (Calcagnotto et al., 2002), down-regulation of $GABA_A$ receptors (Prince et al., 1997) or decreased neuronal sensitivity to GABA (Benardete and Kriegstein, 2002).

The aim of the current study was to measure the profiles in large MCD of GABA+ and GLX concentrations together with concentrations of the other main MRS visible metabolites.

Materials and methods

Subjects

Fifteen controls (seven female, with median age 27 years and range 18—40 years) and 15 subjects with MCD (five female, with median age 30 years and range 21—51 years) were studied. Ethical approval by the Joint Research Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery was obtained, and all subjects gave informed consent. All 15 patients had refractory focal epilepsy, and were taking one or more AED. Diagnosis was based upon full clinical assessment, interictal ± ictal scalp EEG, neuropsychometry and MRI. All control subjects had normal MRI on visual inspection. All patients had a single dominant MRI evident MCD (Table 1). Four had bilateral and symmetrical pathology. In two of these, voxels were placed in homologous regions in both hemispheres and the obtained results averaged. Six subjects had MRI appearance of polymicrogyria (PMG) while nine subjects had MRI appearance of heterotopia (HT).

Magnetic resonance imaging

A 1.5 T SIGNA Horizon Echospeed scanner (General Electric, Milwaukee, WI) with a standard quadrature head coil was used for all studies. Axial T_1 weighted inversion-recovery prepared fast spoiled gradient recalled echo (IR-FSPGR) images were acquired (TE/TI/TR = 4.2/450/15.5 ms, flip angle 20°; matrix 256 × 160; FOV 24 cm; slice thickness 1.5 mm) to guide voxel placement and for segmentation into fractional grey matter, white matter and cerebrospinal fluid (CSF) using SPM99 (Statistical Parametric Mapping; Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London). All MRI studies were reviewed by two experienced neuro-radiologists.

Magnetic resonance spectroscopy

For each MCD patient a voxel was prescribed from the axial IR-FSPGR images with in plane dimensions 40 by 35 mm and thickness 25 mm. The voxel was centred over the major visible MCD (Figure 1). In the controls a single voxel with dimensions 35 mm × 40 mm