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The effect of epileptic seizures on proton MRS visible neurochemical concentrations

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Summary
Purpose: To investigate post-ictal changes in cerebral metabolites.
Methods: We performed a longitudinal quantitative proton magnetic resonance spectroscopy (MRS) study in 10 patients with epilepsy and 10 control subjects. The patients were studied on two occasions: immediately following a seizure, and on a second occasion at least 7 h after the most recent seizure. Each study measured *N*-acetyl aspartate plus *N*-acetyl aspartyl glutamate (NAAt), Creatine plus phosphocreatine (Cr), Choline containing compounds (Cho) and glutamate plus glutamine (GLX) concentrations using a short-echo time sequence (TE = 30 ms), and NAAt, Cr and lactate using a second sequence with longer echo time (TE = 144 ms). The control group was studied on two occasions using the same sequences.
Results: No inter-scan differences were observed for the control group. NAAt and NAAt/Cr levels were lower in the patient group at both measured TEs but did not change significantly between studies. The ratio of Cr at TE 144 ms to TE 30 ms (Cr_{144}/Cr_{30}) and GLX/Cr were higher and Cho lower in the post-ictal scan compared to the inter-ictal study. Change in Cr_{144}/Cr_{30} and $NAAt_{144}/Cr_{144}$ correlated with the post-ictal interval. Lactate measurement at longer TE was not informative.
Discussion: Proton MRS is sensitive to metabolite changes following epileptic seizures within the immediate post-ictal period. The ratio Cr_{144}/Cr_{30} is the most sensitive measure of metabolic disturbance and is highest in the post-ictal period but appears to normalise within 2 h of the most recent seizure.

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Introduction

Proton magnetic resonance spectroscopy (MRS) is sensitive to metabolic dysfunction in patients with epilepsy (Cendes et al., 1994; Connelly et al., 1994; Duncan, 1996; Kuzniecky et al., 1998; Li et al., 2000; Mueller et al., 2002; Woermann et al., 1999). The main visible metabolites, *N*-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr) and choline containing compounds (Cho) are the most commonly reported but glutamate plus glutamine (GLX) (McLean et al., 2000; Savic et al., 2000), gamma-amino butyric acid (GABA) (Petroff et al., 2000) and myo-inositol (Ins) (McLean et al., 2000; Wellard et al., 2003) can also be measured and may be abnormal in patients with epilepsy.

The most common abnormality reported in epilepsy patients is reduction in levels of NAA or NAA/Cr. Reduced NAA has been taken to represent neuronal loss or dysfunction whilst Cr has been considered to represent an internal standard. Low NAA (or NAA/Cr) has been regularly reported in temporal lobe epilepsy (TLE) with or without hippocampal sclerosis (HS) (Cendes et al., 1994, 1995; Kuzniecky et al., 1998). Abnormalities in these parameters have also been noted in the contralateral temporal lobe and in other lobes (Li et al., 2000; Mueller et al., 2002; Simister et al., 2002; Woermann et al., 1999). Levels appear to normalize in these locations following anterior temporal lobe resection and remission from seizures (Hugg et al., 1996).

Studies with human patients have usually been performed inter-ictally and at least 24 h after the last seizure. In these patients there appears to be no correlation between NAA, NAA/Cr or GLX and seizure control, or interval since the most recent seizure (Simister et al., 2002, 2003). GABA levels may rise after administration of several common antiepileptic drugs (AEDs) and with improved seizure control (Petroff et al., 1996, 2001).

The few ictal or post-ictal MRS studies performed in humans have given differing results. Ictal elevation in lactate is the most common observation. NAA may be reduced or unchanged whilst the choline signal may be increased (Lazeyras et al., 2000; Mueller et al., 2001). Post-ictally dynamic changes may be apparent, with evidence of increased mobility of choline (Flugel et al., 2006; Maton et al., 2001) or transient generalized reduction in all measured metabolites (Wellard et al., 2004). In animal studies reduction in Cr and elevation in NAA/Cr, GLX and lactate have been reported, shortly following stimulated seizures (Najm et al., 1997; Neppl et al., 2001). Phosphorous MRS has demonstrated acidosis and reduction in phosphocreatine together with stable ATP levels during status epilepticus (Petroff et al., 1984; Young et al., 1985).

The Cr signal visible to proton MRS is the sum of creatine and phosphocreatine. In mammals ATP levels are tightly controlled (Eq. (1)) using phosphocreatine as an energy store. The relative contributions of creatine and phosphocreatine to the combined Cr signal might therefore be expected to change dependent on the energy demands on the studied system. During periods of high energy demand and increased utilization of ATP, Eq. (1) will be driven to the right to restore ATP levels and reduce phosphocreatine stores.

$$\text{ADP} + \text{phosphocreatine} \leftrightarrow \text{ATP} + \text{creatine} \quad (1)$$

Table 1 Clinical data for the patient group

Patient no./age (years)/gender	Diagnosis	AEDs	MRI	Post-ictal scan		Inter-ictal scan	
				Time from end of seizure to scan (min)	Duration of seizure (min)	Time since last clinical seizure (h)	Time since post-ictal scan (h)
1/28/F	Right TLE	LTG, CLB	Normal	60	4	34	34
2/32/F	Left PLE	VGB, CLB, GBP, LTG, CBZ	Left parieto-occipital MCD	60	2	24	24
3/23/F	Right OLE	VPA	Posterior heterotopia	35	2	48	72
4/23/F	Left FLE	CBZ, GBP	Left frontal MCD	25	2	9	816
5/63/M	Left TLE	GBP, VPA, CLB	Left HS	120	4	72	72
6/45/M	Right TLE	PRM, GBP, LEV LTG, CLB	Right HS	50	1	24	24
7/33/M	Right FLE	CBZ, CLB	Normal	120	1	26	26
8/45/F	Right X-TLE	CBZ, PRM	Multiple WM lesions	120	3	7.5	48
9/32/F	Right TLE	LTG, LEV	Normal	70	1	24	24
10/26/M	Right TLE	CBZ, LEV	Right HS	45	2	48	48

M = male; F = female; CBZ = carbamazepine; CLB = clobazam; DZP = diazapam; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; PHT = phenytoin; PRM = primidone, VGB = vigabatrin; VPA = sodium valproate. FLE = frontal lobe epilepsy, OLE = occipital lobe epilepsy, PLE = parietal lobe epilepsy, TLE = temporal lobe epilepsy, X-TLE = non-localised extra temporal lobe epilepsy. HS = hippocampal sclerosis, MCD = undifferentiated malformation of cortical development and WM = white matter.