Cerebral H-MRS correlates of painless diabetic neuropathy

R. Gandhi[1], D. Selvarajah[1], C. J. Emery[1], P. D. Griffiths[2], S. Tesfaye[1], and I. D. Wilkinson[2]

[1]Diabetes Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom, [2]Academic Radiology, University of Sheffield, Sheffield, United Kingdom

Introduction: Pain is the most distressing symptom of peripheral diabetic neuropathy (DN). Although clear pathological abnormalities have been identified at the level of the peripheral nerve and spinal cord (1), there is only limited understanding of why some patients suffer severe chronic pain whilst others have painless symptoms. Previous proton spectroscopy (H-MRS) studies have demonstrated abnormalities within the thalamus in patients with DN (2). However, it is unclear which parts of the brain's sensory matrix are involved. This large study used H-MRS to determine the neurochemical constitutional make up of the thalamus and the primary somatosensory cortex in the context of DN.

Methods: The cohort consisted 130 subjects: 110 with type 1 diabetes (20 no DN, 30 subclinical DN, 30 painful DN and 30 painless DN) plus 20 healthy volunteers (HV). All subjects underwent detailed clinical and neurophysiological assessments (Dyck's NIS(LL)+7 staging criteria) (3). Single voxel (1.5x1.5x2 cm^3) proton spectra were obtained at 1.5T (Eclipse, Philips Medical Systems, Holland) from the left posterior-lateral thalamic nucleus and left primary somatosensory cortex. At each anatomical location, 2 spectra were obtained: one using a point-resolved (PRESS) technique at long echo time (TR=1600ms; TE=135ms) and one using a stimulated-echo (STEAM) technique at short echo time (TR=3000ms; TE=20ms, TM=12ms). Long TE results are expressed as ratios under the three prominent resonances: Choline (CHO), Creatine (Cr) and N-acetyl aspartate (NAA) groups. Short TE results are expressed as the areas under the NAA, Cho, Cr and *myo*-inositol (mI) resonances relative to that of unsuppressed water.

Results: In the thalamus, at long TE (Fig. 1), subjects with painless DN had significantly lower NAA/Cr (1.55±0.22 [mean±SD]) compared to other groups [HV (1.80±0.23), no DN (1.85±0.20), sub-clinical DN (1.79±0.23), painful DN (1.75±0.19), ANOVA $p<0.001$]. There were no significant inter-group differences at short TE within the thalamus. In the somatosensory cortex, no inter-group differences were seen at long TE. At short TE (Fig. 2), the painless DN group had lower NAA relative to water signal (0.62±0.08), compared to HV (0.73±0.15) and no DN (0.68±0.13) [p=0.03]. Subjects with painful DN had intermediate levels (0.66±0.10), which did not differ significantly from the other groups. No significant group differences were found for any other metabolites or metabolite ratios.

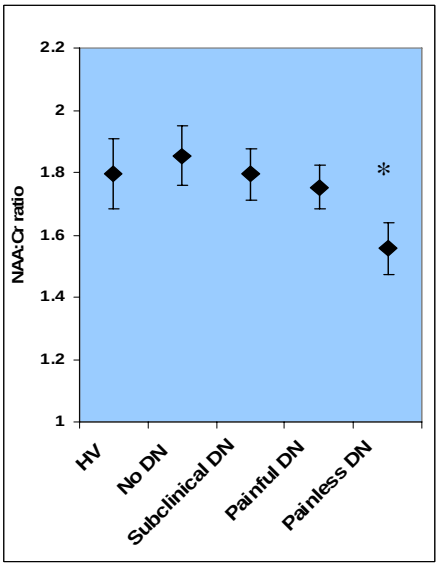

Fig 1. Thalamic NAA/Cr ratio at long TE (135ms)

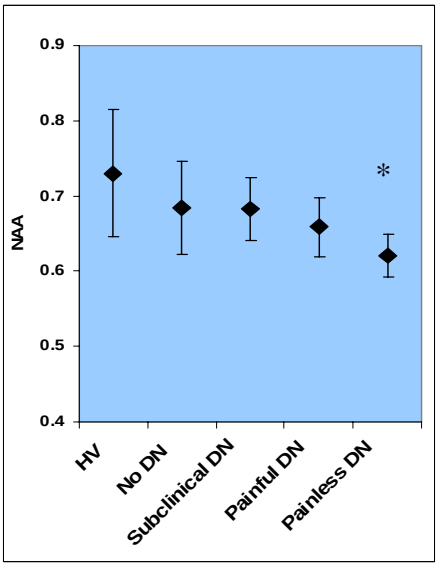

Fig. 2 Somatosensory Cortex NAA relative to unsuppressed water at short TE (20ms)

Error bars represent 95% CI

Discussion: The thalamus is often considered as the sensory 'gateway' to the brain. At long TE, abnormalities may represent changes in neuronal physiology (metabolite relaxation rates) rather than neuronal loss, in painless but not in painful DN. This finding concurs with our previous data from a much smaller sample size (2). Previously documented cerebral H-MRS abnormalities in DN (2) do not appear to occur throughout the brain. It is possible that relative preservation of thalamic neuronal function is necessary for the transmission of abnormal peripheral signals to higher centres and the perception of chronic pain in DN. The results within the somatosensory cortex, in contrast, are suggestive of neuronal loss in subjects with DN and may be reflecting local cerebral parenchymal atrophy which may or may not be a generalised phenomenon. A better understanding of the pathogenesis of painful and painless DN is crucial for the development of novel, targeted, mechanism-based treatments.

References:

1. D Selvarajah et al. Diabetes Care 2006; 29:2664-2669
2. ID Wilkinson et al. Proc ISMRM 200:1532.
2. PJ Dyck et al. Neurology 1997; 49: 229-239.