

Central pain processing in chemotherapy induced peripheral neuropathy

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Background: Whilst modern treatments have significantly extended life expectancy in multiple myeloma, a high incidence of chemotherapy induced peripheral neuropathy (CIPN) has evolved that can result in chronic pain. The exact pathophysiological mechanisms of CIPN, including potential involvement of the brain, remain unknown.

Aim: To determine whether differences exist in central pain processing regions, as assessed by Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) during noxious thermal stimulation, between patients with CIPN and healthy controls.

Method: The cohort comprised 12 patients with myeloma and 12 healthy volunteers. All patients underwent neurophysiological testing to assess nervous system status. Imaging was performed at 3T (Achieva, Philips). Two Blood Oxygen-Level Dependent (BOLD) fMRI datasets were acquired for each subject in a box-car paradigm design: one where heat-pain stimuli were applied to the dorsum of the foot and the other to the thigh. The latter was included as a potential sensory control area. Prior to imaging, a subject-specific heat-pain temperature defined as 7/10 on a Likert psychometric pain scale was determined at each of the 2 anatomical areas. Each fMRI run lasted 600s and comprised presentation of 7 noxious stimuli (duration 30s) interspersed with 7 periods of baseline temperature (32°C, duration pseudo-randomised to 55, 60 or 65s). The fMRI datasets were obtained using a single-shot T2* weighted gradient-recalled, echo planar imaging (EPI) sequence (TE=35ms; TR=3000ms; SENSE encoding factor=1.5; resolution of 1.8mm x 1.8mm x 3mm). After standard pre-processing, the BOLD response to heat-pain was estimated and regions where foot response was greater than thigh response were identified for each subject using the General Linear Model (SPM5). Any differences between multiple myeloma and control groups were then determined.

Results: The neurophysiological tests showed abnormality in myeloma indicative of peripheral neuropathy, mainly in the feet. Painful stimuli delivered to the foot produced significantly greater thalamic response than thigh stimulation in subjects with CIPN when compared with healthy volunteers (stereotactic coordinates: x=-12, y=-24, z=8; peak T=4.64; 239 voxels exceeded height threshold p<0.001, uncorrected) Figure 1.

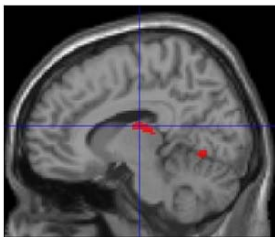


Figure 1: Thalamic differential response between CIPN patients and controls. The areas correspond to greater BOLD response in the foot compared to thigh (neuropathic-affected vs symptom-free sites) being larger in the CIPN group when compared to the control group.

Discussion: CIPN is a very debilitating by-product of chemotherapy. The response to heat-pain was studied at different anatomical sites since neuropathy is known, clinically, to predominantly affect the extremities (feet), leaving proximal areas (thighs) with relatively preserved sensory response. The results indicate that painful stimuli delivered to neuropathic-affected and symptom-free sites in CIPN evoke differential activation of distinct cortical regions when compared to controls, which could reflect abnormal central pain processing. Involvement of the CNS is likely to result in different sensory gating in CIPN and this will have consequences on pain perception, modulation and it may provide novel therapeutic target areas.