Non-freezing cold injury – a multi-faceted syndrome.

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Sir

We read the paper "Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy" by Vale and colleagues recently published in Brain with great interest. Despite the impact non-freezing cold injury (NFCI) can have on an individual's quality of life, little research has been conducted on this condition. Indeed, in the last 10 years only 16 full papers have been published on NFCI, of which six were reviews, four were epidemiological studies, two were case studies and only four were original research articles. The research articles, like the range of proposed pathogenesis and reported symptomology of NFCI, vary considerably: one reported data collected 30 years ago on Royal Marines involved in the Falklands Campaign (Golden *et al*. 2013), another related to an animal model of NFCI (Geng *et al*. 2015), a third focussed on vascular dysfunction in NFCI (Eglin *et al*. 2013), whilst Vale *et al*. (2017) concentrate on the neuropathy associated with NFCI. Whilst we are encouraged by further advances in our understanding of NFCI offered by this paper, we feel that it is important to highlight some limitations of this study in an area that has become blighted by repetition of un-founded speculation and uni-disciplinary investigation.

In the study of Vale *et al*. (2017), participants were recruited on the basis of experiencing pain in their hands or feet. In contrast, only 48% of the Royal Marines with NFCI from the Falklands Conflict reported pain (Golden *et al*. 2013). This suggests that Vale *et al*. (2017) were investigating a sub-set of NFCI patients and therefore their finding that 95% had sensory neuropathy compared to the 35% reported by Golden *et al*. (2013) was not surprising and a little circular.

Intraepidermal nerve fibre density was measured in biopsies taken 10 cm proximal to the lateral malleolus - an area in which the participants did not suffer pain (see Figure 2A), and in which NFCI symptoms are rarely reported. The reported reduction in nerve fibre density correlated with heat pain threshold but with none of the other sensory measures. Therefore, its use in explaining the "cold hypersensitivity" reported by the participants and its value in diagnosis of NFCI are unclear.

The control participants for this study were matched for age, gender and ethnicity but not for physical fitness or cold exposure. In addition, they were living in a different country from the cases. Therefore, it is not known whether the altered nerve fibre density reflect the effect of physical training and cold exposure independently of NFCI. In terms of diagnostic specificity, it is important to know whether individuals with NFCI not reporting neuropathic pain can also demonstrate the changes in nerve fibre density reported by Vale *et al*. (2017); this requires testing a broader cohort of NFCI patients. For example, many individuals exposed to cold conditions as part of their recreational activities are cold sensitive but are not considered to have NFCI (Eglin *et al*. 2017; Hope *et al*. 2014). Whilst the participants self-reported cold hypersensitivity in the study by Vale *et al*. (2017), this was not examined objectively. In our study (Eglin *et al*. 2013) examining rewarming following a standardised extremity cooling protocol in patients with NFCI, 14 of the 22 patients were cold sensitive with the remaining eight showing a normal response, thus highlighting the heterogeneity of NFCI symptoms.

It is interesting to note that the sympathetic skin responses were measured in the study by Vale and colleagues with a skin temperature above 32 °C. In our study, we found that despite 30 min rest followed by 12 min exercise in a room at 30 °C, toe skin temperature in half of the participants was still below 32 °C and in seven was below 30 °C. Again this would point towards a subset of NFCI patients being investigated, unless an aggressive skin warming technique was omitted from the methods section.

BPI pain severity was found to correlate with the sensory sum score which was a composite of mechanical and vibration but not temperature sensation. This seems strange given the reported nature of NFCI.

One of the problems associated with investigating NFCI is the range of conditions (environmental temperature, exposure time, activity level, clothing worn, hydration and nutritional status, fatigue and stress levels) that can result in NFCI. Even in standardised conditions, the 'dose' (temperature and duration) required to cause NFCI (and its variability) is not known. It would appear from Table 1 that the participants studied by Vale *et al*. (2017) suffered a duration of injurious cold exposure which ranged from under 1 hour to over 4 weeks. This wide range in exposure time may have led to a varying degree of damage and of NFCI characteristics. Unfortunately, correlations between duration or severity of cold exposure and severity of symptoms or measures of nerve fibre density, pain or sensory testing are not reported.

It was reported that all of the participants had had a change in their employment status since receiving their NFCI. This begs the question as to whether any of their participants were seeking compensation from the MoD and it was therefore in their financial interest to report severe symptoms.

In conclusion, we congratulate Vale *et al*. (2017) on a first class investigation of the neuropathic aspects of NFCI patients reporting neuropathic pain and acknowledge many of the limitations of the study were unavoidable. However, the paper also highlights the urgent need for an objective, evidence-based test or more likely a battery of tests for diagnosing NFCI. This will only be obtained through conducting high quality research examining **both** the neural and vascular aspects of NFCI in a wide range of patients, and comparing them to an appropriate control population matched for ethnicity, sex, age, physical fitness and cold exposure (i.e. individuals who have undergone the same military training but have not got a NFCI).

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