

Non-freezing cold injury? a multi-faceted syndrome

Dear Prof Kullmann,

We thank Eglin *et al* for their thoughtful commentary on our manuscript, in which we undertook the first detailed neurological assessment of persistent symptoms following non-freezing cold injury. Whilst we stress that sensory neuropathy is one core feature of NFI we do not want to give the impression that vascular factors may not play a role. In fact, given the intimate relationship between peripheral neurons and blood vessels in the neurovascular unit, it would be a surprise if vascular changes were not observed.

In response to the point that we studied a sub-set of NFI patients we intentionally focussed on chronic NFI. One of the difficulties encountered in the NFI literature is the lack of case definition, and of the papers quoted in Eglin's commentary, our manuscript is the only one which explicitly defines what constitutes a case of chronic NFI (which is the major cause of morbidity). We used a pragmatic case definition of sensory symptoms (not just pain) beginning at the time of exposure and persisting for at least 3 months. There is no 'circular logic' in this approach: in a cohort study the starting point should be defining what your cohort consists of.

These issues are well illustrated in the paper by Golden *et al.*, with which Eglin *et al.* make comparisons to our study. In that study a postal questionnaire was sent to personnel who had fought in the Falklands conflict (6-10 weeks following the end of hostilities). A subset was then invited for further investigation. In Golden's manuscript the patients only had to have sensory or trophic symptoms "for a couple of days" to make a diagnosis of NFI and there was no specification of temporal relationship to cold exposure. Nerve conduction studies were performed but methods do not describe which nerves were tested or what criteria were used to decide if they were abnormal (and as we show, these are very insensitive compared to skin biopsy). The assertion made that 35% of the Golden *et al.*-cohort had a sensory neuropathy is simply not supported by the data. Finally, and most importantly, although tests such as infrared thermography are used by Golden *et al.*, (the utility of which is debated), medical examination was stated by the authors as " cursory". We have shown that over 90% of patients had abnormalities on detailed neurological examination in a pattern typical of a sensory neuropathy affecting the extremities.

Eglin *et al.* are concerned that skin biopsy is performed 10cm above the lateral malleolus, which is proximal to the most severe symptoms. This was a condition of our ethical approval and is also the internationally accepted standardised site for skin biopsy for the investigation of small fibre neuropathy. This apparent paradox is true of many small fibre neuropathies causing pain in the feet, however its use has been well validated as a sensitive and specific measure of sensory neuropathy (please read Lauria *et al.*, 2010 for a detailed review).

There appears to be some misunderstanding of what we mean by the term "cold hypersensitivity", a symptom we defined in our manuscript as "exacerbation or emergence of symptoms in cool or cold conditions". Eglin *et al* (2013) confuse this symptom both with quantitative sensory testing (see Vale *et al.*, discussion) and with their own work in which they assess how quickly an extremity rewarms following cold water immersion, entirely different contexts, which are not interchangeable. All the participants in our study complained of the symptom of cold hypersensitivity. Mean foot

temperature for participants undergoing QST is reported in supplemental data and is 28.6 °C (i.e. comparable with their own findings in NFI subjects).

Misconceptions regarding the sensory symptoms of NFI are also illustrated by Eglin et al.'s statement "it seems strange given the reported nature of NFI [that pain severity correlates with sensory sum score]". The earliest descriptions of NFI symptoms included a mixture of small and large fibre modality deficits including numbness, paraesthesia and pain (i.e. not *just* cold hypersensitivity) (Smith et al., 1915), a point which we confirmed in the paper (see figure 2). The sensory sum score includes examination of small (pin prick) and large fibre (light touch, vibration and proprioception) function. It is entirely logical to us, therefore, that there should be a correlation between pain intensity and the sensory sum score, as has been shown in other painful neuropathies (Themistocleous et al., 2016).

We agree with many of the points that Elgin et al. make about directions for future studies/improvements. We would like to study service personnel exposed to the cold who are asymptomatic and await such cohorts being made available by the MoD. Longitudinal studies would provide fascinating data on why the symptoms resolve in some service personnel but not others. A key future step in coordinating research and clinical pathways on NFI is the adoption of a clear case definition. To conclude we think vascular changes in NFI are an important area of future research but we have provided compelling evidence that the majority of patients with persistent sensory symptoms following NFI have a sensory neuropathy. Their neuropathic pain should be assessed and treated appropriately. Assessment should not simply be a "battery of tests" but what has hitherto been most lacking is detailed clinical assessment, which is so often the most useful diagnostic tool that we have.

Yours sincerely,

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References

Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, Nolano M, Merkies IS, Polydefkis M, Smith AG, Sommer C, Valls-Solé J; European Federation of Neurological Societies; Peripheral Nerve Society. Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. *Eur J Neurol*. 2010 Jul;17(7):903-12, e44-9. doi: 10.1111/j.1468-1331.2010.03023.x

Smith JL, Ritchie J, Dawson J. On the pathology of trench frostbite. *Lancet* 1915; 186.

Themistocleous AC, Ramirez JD, Shillo PR, Lees JG, Selvarajah D, Orengo C, Tesfaye S, Rice AS, Bennett DL. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain*. 2016 May;157(5):1132-45.

Vale TA, Symmonds M, Polydefkis M, Byrnes K, Rice ASC, Themistocleous AC, Bennett DLH. Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy. *Brain*. 2017 Oct 1;140(10):2557-2569. doi: 10.1093/brain/awx215.