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Title
DYNAMIC MECHANICAL ALLODYNIA FOLLOWING FINGER AMPUTATION: UNEXPECTED SKIN HYPERINNERVATION
Authors:
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Dear Editor,

Please find enclosed the answers to the queries of the reviewers.

Sincerely yours,

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REVIEWER 1

Comment
The significance of the current case report would be greatly improved if the images from the fluorescence microscope system indicating the difference in innervation between normal skin and allodynic skin.

Response
We added the figure, as suggested.

Comment
Abstract: ...sensation evoked by gentle stroking the skin. Should be "sensation evoked by gently stroking the skin"

Response
We modified the text, as suggested.

Comment
Abstract: "In conclusion, neurodiagnostic skin biopsy might represent an useful tool for derangements..." please rephrase the sentence as "In conclusion, neurodiagnostic skin biopsy might represent an useful tool for detecting derangements..."

Response
We modified the text, as suggested.

REVIEWER 2

This case presented with a 53-year-old female patient who complained of severe tactile allodynia in her hand after amputation, and the authors concluded from the patient that epidermal hyper-innervations is a possible reason for this situation. I have some concerns on this topic:

Comment
1. The paper focused on skin innervations after nerve injury, for this condition, some evidence showed it was yes, but some said no. For animal studies, the epidermal hyper-innervations occurred but without original order. In fact, this patient belongs to neuropathic pain after amputation, so the treatment should be concentrated on central nervous system blockade. Yes, capsaicin is a choice, but its effectiveness is limited.

Response
a) We agree on the possibility to observe, after a nerve injury, different patterns of skin innervation and think that the finding of an abnormal epidermal innervation described here cannot indeed be generalized to all cases of nerve injury.
b) We also agree on the frequent loss of original innervation order and underlined it in figure 2, showing the abnormal regeneration of some nerve fibres in the dermis of allodynic skin.
c) Although a central sensitisation does occur in several cases of peripheral nerve lesions, in our opinion central nervous system blockade cannot be considered the most important treatment for neuropathic pain after amputation. We think that, considering that the central sensitisation is always triggered by peripheral mechanisms, if an effective therapy targeted on peripheral mechanism is possible, this therapy is able to reverse also central sensitisation phenomena.
d) We agree on the evidence that capsaicin is only one therapeutic choice, not useful in any cases. The problem is in the difficulty to predict the antalgic effect and adequately select the patients before

treatment. The case presented here suggests a possible selection based on the finding of an epidermal hyperinnervation.

Comment
2. The authors used fluorescent biopsy for the skin, but they did not show any figures on this. I suggest this should be included for the case presentation. Also which kinds of markers were used for the biopsy also needs to be clarified.

Response
As suggested, we added the figure and specified in its legend the markers used.

Comment

3. Central sensitization after peripheral nerve injury is a potential mechanism, please discuss this why it is merely from peripheral innervations, but not central mechanisms.

Response
We have already discussed this point in a previous response to a comment .

Comment

4. For the patient, I noticed that she underwent several times of surgeries for removing the neuromas of the digital nerves to her index finger. This is an indicator that the patient's repeated surgery also contributed to her persistent pain because present evidence showed that repeated injury no matter incision or nerve injury, it would increase the chance to develop chronic pain.

Response

We completely agree on the observation that repeated surgery increases the chance to develop chronic pain, but this not means that it is impossible to find the pathophysiological mechanism of the painful condition and provide an effective pain therapy targeted on that mechanism. In the case presented here the unexpected finding of an epidermal hyperinnervation pushed us to consider it a possible pain mechanism and to try to denervate the epidermis by capsaicin in order to better manage the patient's pain.