Author's response to reviews

Title: Central poststroke pain: somatosensory abnormalities and the presence of associated myofascial pain syndrome.

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Author's response to reviews: see over
RESPONSE TO REVIEWERS

We thank the journal editors and the reviewers for all the care and attention devoted to our work. The suggestions helped improve our work. We agreed with all comments made by the reviewers and changed the text accordingly. Below are our responses to each reviewers’ comments.

Reviewer's report 1

Title: Central poststroke pain: somatossensory abnormalities and the presence of associated myofascial pain syndrome.

Version: 3 Date: 28 February 2012

Reviewer: Henriette Klit

Reviewer's report:

This a interesting article looking at the prevalence of myofascial pain syndrome (MPS) in 40 patients with CPSP. Other post-stroke pain (PSP) conditions are common in patients with CPSP and may influence the treatment. Making the differential diagnosis between CPSP and other concomitant PSP conditions is often difficult and not much research has been done in this field. Therefore this is an interesting topic, but unfortunately the authors do not explain in detail how MPS was diagnosed.

The authors find a very high prevalence of MPS in the patients. The question is whether this is a direct consequence of the stroke or is related to motor deficits. Unfortunately this is barely discussed. Nor is there a control group, so the prevalence of MPS in stroke patients with other PSP pain conditions is not known. A clear distinction between CPSP and PSP in not made in the paper.

- Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.
1. Abstract and conclusion. "MPS is frequently under-diagnosed in CPSP patients. Its presence has important therapeutic implications and can improve the clinical outcome when identified and treated."

-This paper suggests that myofascial pain syndrome (MPS) is common in patients with central post-stroke pain (CPSP) and may be under-diagnosed. Unfortunately there is no control group, so it is not possible to say if this condition is more common in patients with CPSP as compared to other pain patients, patients with PSP or stroke patients with the same amount of motor deficits.

*We agree with reviewer 1 that due to the uncontrolled design of the study one cannot attest that the prevalence of MPS is higher in CPSP than in pain free stroke patients, or in other PSP syndromes. We have changed the text accordingly. Our main aim was to draw attention of the readers to the fact that despite the high prevalence of MPS in this population this issue had never been addressed before. We agree that the presence of MPS could be related to motor deficits. Here we have included a supplementary analysis comparing the prevalence of pyramidal signs and the presence of MPS, we found a non-significant association (Chi2 = 1.91; P=0.170). This data were included in the text. Although not definitive, this would argue against such an association of factors. (see conclusions in the abstract and in the main text)*

2. Abstract and conclusion. "Its presence has important therapeutic implications and can improve the clinical outcome when identified and treated. " -I do not think the authors have the evidence to support the statement that identification and treatment of MPS can improve the clinical outcome. In contrast, the report that patients CPSP patients with and without MPS did not differ in pain intensity, MPQ or BDS, indicating that MPS does not play an important role by itself.

*We agree with the reviewer. We intended to say that the detection of MPS in general (ie. other pain syndromes such as in fibromyalgia and low back pain) has important therapeutic implications, and we speculated if the same would apply to CPSP. We agree that the lack of difference between the VAS, BPI and
MPQ did not differ between patients with and without MPS is an argument against this hypothesis. This sentence was suppressed from the text.

3. Abstract and conclusion. "The presence of MPS is not an exception in CPSP and should be accepted as part of its spectrum of clinical presentation". I disagree with this statement. Although MPS seems to be common in patients with CPSP, it is not necessarily a part of the CPSP spectrum, while MPS should perhaps be accepted as a part of the spectrum of post-stroke pain (PSP). Central neuropathic pain is defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the central somatosensory nervous system”. This implies that only pain directly due to the lesion in the CNS can be classified as central neuropathic pain. Central post-stroke pain (CPSP) is a central neuropathic pain condition where the underlying disease is the stroke. In contrast, post-stroke pain (PSP) is a term used for all types of pain conditions seen in stroke patients, including CPSP, poststroke shoulder pain and other musculoskeletal pain conditions. A clear distinction should be made between pain conditions due directly to a lesions of the CNS and peripheral pain conditions involving central mechanisms. As such, if a myofascial pain syndrome (MPS) is found in a stroke survivor, this can be classified as PSP, but not as CPSP (Klit, H., Finnerup, N.B., Jensen, T.S., Central post-stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurology 2009, vol 8 (9):857. For discussion see: Roosink, M., Geurts, A.C., Ijzerman, M.J. Defining post-stroke pain: diagnostic challenges. Lancet Neurology 2010, vol 9(4):344 and Klit, H., Finnerup, N.B., Jensen, T.S. Author's reply. Lancet Neurology 2010, vol 9(4):344). In stroke patients with pain, several pain types might be present in the same area of the body and it can be difficult to separate central neuropathic pain from other types of PSP. The differential diagnosis is based on the sensory findings, location of the lesion, and specific findings on clinical examination. In the case of MPS, such findings may include taut palpable bands in the muscles, distinct patterns of referred pain, satellite trigger points and a limited range of movement.
We totally agree with reviewer 1 on the distinction between PSP and CPSP. Our main point, and we took in this paper MPS as an example, is that the proposed definition of CPSP as a diagnosis of exclusion should be rethought since “pure” CPSP may represent smaller subgroup of patients (1/3 of our sample) not representative of the whole CPSP population if one accepts that other pain syndromes may coexist in the same patient, as is frequently the case in clinical patients. All patients in the study had defined neuropathic pain according to the IASP definition. The point was to raise the discussion on the necessity to consider as CPSP only those who did not present any other pain syndromes (i.e., a diagnosis of exclusion). Of course, this is simply a hypothesis to stimulate the discussion on this interesting topic. We have changed the terms in text to avoid misinterpretations.

The absence of a control group has been commented in the limitations of the study.

Please see

Page 11, last three paragraphs

Page 12, second paragraph.

3. Background. MPS is not defined in this section. How was it defined? How common is it in other pain populations or controls? Since one of the major conclusions of the article is, that MPS is very common in CPSP, these are necessary informations in order to evaluate the findings.

We have placed MPS definition in “Backgrounds”:

Please see: page 4, second paragraph

4. Methods, clinical investigation. “MPS was defined by the appearance of pain of identical characteristic, referred pattern, and cutaneous manifestations after the palpation of an active trigger point[20] in one of the predefined muscles”
This is unclear to me. What is meant by identical characteristics? Which predefined muscles? Was there a minimum pain score or rating system. The authors need to more clearly explain how MPS was defined.

We have rephrased the text.

Please see: page 7 lines 10-12.

5. Figure 1. Unfortunately, the quality of the available online artwork was not high enough to evaluate the figure. I think it is important to include the figure in the paper (in proper quality).

We have attached a picture with higher quality

Please see: figure_1

Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

1. Background, reference

I do not know the cited article, but usually the reference for this statement is made to this article: Edinger L: Giebt es central antstehender Schmerzen?. Dtsch Z Nervenheilk 1.262-282.1891

The reference was changed,

Please see: page 15 1st reference.

2. Background, “…it has been recently proposed that CPSP should be a diagnosis of exclusion, uniquely reserved for patients with PSP and no other pain syndromes[17].”

-I do not quite agree with this statement. In our review (ref 17), we suggest some diagnostic criteria for CPSP which include that “Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely”. We never said that other pain syndromes could not be present, in fact,
we do state in the article, that the presence of other concomittant PSP conditions is common in patients with CPSP (Klit et al, Lancet Neurol 2009).

We agree with the cited revision (17) that “identifying a central neuropathic element to the hemiplegic shoulder pain, spasticity or other musculoskeletal pain might be difficult and in some cases, several pain types might be present in the same area of the body” and the findings of this study corroborate this view. However, we do not see the diagnosis of CPSP as one of exclusion, as stated in panel 4 of the cited review (first topic of the diagnostic criteria for defined CPSP). We understand that such a restrictive definition gains in specificity but it may lose in sensibility. The high prevalence of MPS in this population, and the fact that it does not impinge a more severe pain clinical picture (similar VAS, MPQ) speaks for this idea. Of course, larger controlled studies are necessary to confirm this view and to shade light on the interplay between CPSP and the other pain syndromes that may be part of the broader PSP scenario.

We have made all changes according to the suggestions: Please see 11 from line 4 through second line of page 12.

3. Background. “Although apparently sound, this proposal must be tested, since it is not known to which extent CPSP overlaps with other PCP syndromes such as MPS.

Should read PSP not PCP.

It has been changed.

4. Methods. Inclusion criteria. “Inclusion criteria were adults (> 18 years), presenting chronic definite neuropathic pain[16]...”

For clearification, the authors do mean definite central neuropathic pain?

The text was revised:

Please see page 6 line 6

5. Methods, clinical evaluation. “Patients were taught about the characteristics of their neuropathic pain.”
Patients were interviewed?

The text was not clear and was changed.

Please see page 6, second paragraph.

6. Results and discussion. “Thirty-six (90.0%) patients had one single ischemic stroke. Six (15%) had more than one vascular event.”

- This gives a total of 42 patients, not 40.

There were 36 (90.0%) patients with at least one ischemic stroke. We used “Vascular event” as a general term that included both ischemic and hemorrhagic strokes. Thus, these terms do not exclude each other. We have made the text more clear.

See page 8, results.

7. Results and discussion. “Mean pain intensity was 89±14mm (51-100).” Since pain intensity is clearly not normally distributed in this sample, I suggest the use of percentiles instead of standard deviations here. Is this the present pain intensity or the mean pain over time?

It is the present pain intensity. we have also included the average pain time interval:

We agree. We have changed means into median (range) pain intensity and also have included average pain time, which is more accurate when dealing with non-parametric data.

See page 9 line 6

8. Discussion. “Interestingly, despite the obvious implication in treatment and rehabilitation, the presence of MPS was not associated with more intense pain or pain associated mood disorders in CPSP patients. This is a strong argument for a reappraisal of the current CPSP definition.[17]”

- I do agree that the CPSP definition can probably be improved, but I am not sure I follow the given argument. First of all, the fact that the presence of MPS was not associated with more intense pain or mood disorders may as well point
to the fact that the way MPS was diagnosed in this sample was inaccurate or that the presence of MPS in CPSP patients does not influence their overall pain status or mood. Secondly, it is unclear whether the authors actually used this classification in the paper.

This paragraph has been revised, please refer to page 10, second paragraph; page 11, and to previous responses.

9. Discussion. “It has been recently proposed that CPSP should be a diagnosis of exclusion in PSP patients, despite the absence of published data or clinical experience to backup this proposal. Our data suggest that this proposal will fail to detect more than half of all the individuals with definite central neuropathic pain in this population.”

What is the reference for the first part of this statement? In our review, we suggested that CPSP be a diagnosis of exclusion, not PSP. Also our proposed definition does not exclude patients with other pain conditions, but merely states that the diagnosis of CPSP should only be made when other cause of pain is unlikely. Please see previous comment (#2).

It has been corrected. See page 10 line 19.

10. Discussion. “And more importantly, our data showed that MPS should be viewed as part of the CPSP syndrome complex”.

As I understand it, MPS is due to a peripheral disease, although central mechanism play a role in this pain condition, as in most other chronic pain conditions. MPS should perhaps be viewed as a part of the PSP spectrum, but not as a central pain syndrome as there is not direct relation to a lesion in the CNS.

11. Discussion. “It is prevalent and its presence did not impose pain of higher intensity of more severe interference in this group of patients.” How do the authors explain this? Please elaborate.
We agree with reviewer 1 that MPS should be seen as part of PSP and not CPSP. Our point was to indicate that MPS may co-occur with CPSP quite frequently. The have been revised, please see page 11 and page 12.

12. Discussion. “In short, neurovegetative signs may be epiphenomenal in CPSP patients.”

I disagree. In my experience autonomic signs are quite rare in CPSP patients in my country (Denmark), whereas it has been reported to be quite common in e.g. Turkey. I think the extent of autonomic dysfunction has to do with the degree of immobilisation and physical therapy. Also, in some conditions, an autonomic finding may be directly caused by the stroke, as e.g. a Horners syndrome I lateral medullary infarcts. Some authors have reported autonomic dysfunction as a part of MPS, but this is not discussed in the paper.

We also think on the autonomic signs as part of immobilization or neural deficits itself. The text have been revised. See page 12; line 10

13. Discussion. The use of treatment is not discussed. Do the patients receive pain medication. What kind? Are they taking any antidepressants or antiepileptics that may reduce the pain from CPSP? Or NSAID? Can this have influenced on the pain score? Do they receive other kinds of treatment that might influence the MPS, such as massage or acupuncture? 14. Table 1. what is hypopalexstesia? Please define or use another word.

All patients were treated with first and second line drugs for neuropathic pain. We have added a paragraph with the medications used, which are also summarized in Table 1. At the time of the study, some drugs were not yet available in our country public health system (eg lamotrigine, pregabalin, venlafaxine, and duloxetine) Chlorpromazine, despite of all safety concerns an unproven efficacy in neuropathic pain, was used in patients under 70 years old. A follow up evaluation on VAS of pain after 1 year of treatment have been made and added to the text. Only five patients were on regular physical therapy and six received acupuncture.
Hypalgesia refers to decreased vibration detection threshold and was changed on the text.

Please see page 8, 2nd paragraph

Please see table 1, and limitations of the study on page 11.

Discretionary Revisions

These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.

1. Background. Last line “...to assess the presence of other non-neuropathic pain syndromes, and in particular, the role of myofascial pain syndrome in this sample.”

Since only MPS is reported in the paper, the authors should consider revising the sentence.

The phrase has been revised:

Please see page 10 second paragraph.

2. Methods/table 2. The authors should consider revision the section on the sensory examination, so that it fits better with the table. E.g. hyperalgesia was tested using pinprick.

The text was revised:

Please see page 7 line 2

3. Discussion. “This finding could be a consequence of the magnitude of themotor deficits and spasticity.”

I think this a very valid and important point. If at all possible, the authors should try to report the degree of motor deficits of the paitents and correlate it to the presence of MPS.

The discussion has been revised:
Please see page 11 line 5 through page 12 line 8

4. I would like to see a table included in the supplementary material of the paper summarizing the duration of pain, time from stroke to onset of pain, location of stroke, concomitant diseases, and treatment of each patient.

These data have been added

Please see table 1

Please see page 8 line 7

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer's report

Title: Central poststroke pain: somatosensory abnormalities and the presence of associated myofascial pain syndrome.
Reviewer´s report 2

Version: 3 Date: 5 March 2012

Reviewer: Samar Hatem

Reviewer's report:

In this manuscript, the authors examined the incidence of myofascial trigger points in patients with post-stroke central pain. Myofascial pain syndrome (MPS) was found to be frequent after stroke associated with neuropathic pain symptoms. The authors suggest that MPS should be regarded as part of the heterogeneous clinical presentation of central post-stroke pain (CPSP). This manuscript is well-conceived and clearly written. Methodology and statistics are sound. Pain after stroke presents a clinical challenge in terms of etiology and treatment. The data presented in this manuscript deal with the clinical recognition of muscular pain symptoms after stroke which is of obvious clinical interest.

Major compulsory revisions:

1. Abstract: I partially disagree with the conclusion of the abstract. MPS is certainly under-diagnosed in CPSP patients. However, in order to sustain that MPS is a part of the clinical presentation of CPSP, the authors should provide data indicating that MPS is not present in patients without CPSP… In this paper, there is no comparison between stroke patients with and without CPSP. Thus, it could be that MPS is not only part of the spectrum of clinical presentation of CPSP, but that MPS is actually present in stroke patients without neuropathic pain symptoms at all. Less than 20% of patients have true central pain after stroke (CPSP), i.e. pain that can be considered exclusively neuropathic (Hansson 2004, Anderson et al. 1995). The rest of the patients is not pain-free, but may present nociceptive pain, such as MPS. The conclusion of the abstract and of the manuscript should be rephrased.

We agree with reviewer 2. The abstract has been revised,

Please see page 3 line 5
2. Results and Discussion: Shoulder-hand syndrome is not caused by the immobilization, but by the motor paresis of the shoulder, which leads to gelnohumeral joint subluxation. Immobilization is avoided in stroke rehabilitation.

The text has been revised,

Please see page 12 line 5

3. Results and Discussion: Concerning depression and antidepressant agents: recent studies have shown that antidepressant drugs such as paroxetin increase motor recovery and functional status in stroke patients. Thus, treating depression does not only improve the quality of life of patients but also the functional outcome (Paolucci et al. 2001; Loubinoux et al. 2002; and several other papers). In particular, the effect of antidepressants on MPS after stroke should be examined.

We included a list of medications used by these patients as well as the VAS after one year of follow-up.

Please see page 8 line 3

Please see table 1

4. Conclusion: as explained in comment #1, I would rather prefer to read that the following in the conclusion “The presence of MPS is not an exception after stroke and may present in association with central post-stroke pain”.

We fully agree with this revision. The abstract and conclusion have been revised.

See page 3 line 5 and page 13 in conclusion

Minor essential revisions:

5. Methods: Could the authors clarify the definition of MPS: what is meant by ‘identical characteristic, referred pattern’?

The text has been clarified as stated above. See page 7 line 10-12.
6. Results and Discussion: How much time had passed since the last stroke event in the patients population? Were there any recent lesions on diffusion MRI?

Data on the stroke pain interval have been added

Please see table 1

Please see page 9 line 3

7. According to the authors, is there any explanation for the preferential localization of trigger points above the pelvic girdle? Why were so few muscles of the lower limb examined?

The main muscle chains were systematically evaluated in these patients, as base on a pilot evaluation performed before the study began. However it is true that most trigger points were located above the waist. We tried to look at the role of motor deficit/pyramidal tract lesion and the presence of MPS, an correlation analysis was included in the text, but we found no association between these variables. This topic remains to be elucidated in future studies.

8. Table 1: Could the authors explain what is meant by ‘undetermined’? Was the brain imagery unavailable? This is unfortunate because this subgroup presents with MPS in more than half of cases.

Brain images were available for all 40 patients (24 MRI and 16 CT scans). The group undetermined refers to the group of 5 patients with a vascular lesion affecting the somatosensory system in more than one location (ie. cortex and subcortical regions, lateral thalamus and internal capsule).

Minor issues not for publication:

1. Title : ‘somatossensory’ should be ‘somatosensory’

   Title has been corrected

2. Abstract : ‘classed’ should be ‘classified'
Abstract has been corrected, see page 2, line 14.

3. Methods: ‘stroke’ should be ‘stroked’

4. Methods: ‘CSPS’ should be ‘CPSP’

5. Methods: ‘marked and a human body’ should be ‘marked on a human body’

6. Methods: ‘Brain MRI’ instead of ‘Head MRI’

Corrections in methods have been made.

7. Results and Discussion: ‘intensity of more severe’ should be ‘intensity or more severe’

This have been removed from the text

8. Table 3: ‘bracqioradialis’ should be ‘brachioradialis’

It has been corrected.

9. Results and Discussion: ‘finding that in 4 of the 8’ should be ‘finding that 4 of the 8’

10. Results and Discussion: ‘infarct’ should be ‘infarction’

Corrections in Results and Discussion have been made

11. References: #9 ‘centrl’ should be ‘central’

The corrections have been made

12. Figures 1: ‘miofascial’ should be ‘myofascial’

The correction has been made

13. Figure 1 was too small and with bad resolution. I couldn’t find out where the trigger points (+) were on the picture. Could this be improved?

We have uploaded a figure of better quality.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'

Once again we would like to thank the reviewers for the care and time devoted to the comments and observations made to our work.

We hope the manuscript in its current form will merit publications in your journal.

Sincerely

The authors