Reviewer's report

Title: Morphological macrovascular alterations in CRPS demonstrated by increased intima-media thickness

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Reviewer: Floris Schreuder

Reviewer's report:

Derenthal and co-workers have written an appealing article in which they study the intima-media thickness (IMT) in various arteries in patients with type I complex regional pain syndrome (CRPS). The paper is well-formulated, original and relevant. As the authors state, there has not been any previous reports concerning macrovascular changes established by IMT in CRPS. The authors demonstrate that CRPS leads to locally increased IMT, with what it seems a gradient from proximal to distal in the affected hand. They suggest that this is due to previously demonstrated involvement of local inflammatory processes, which have been shown to alter the vessel wall in other diseases such as rheumatoid arthritis. As mentioned in the discussion, they cannot conclude that this observation is due to the supposed inflammatory responses since these were not measured in the present study. In addition, one major confounder is a difference in disease duration between the subgroups. A large point of concern and a possible large confounder may be the fact that the measurements were performed whilst the sonographer was not blinded to the clinical information.

The authors should consider the following points:

- Major Compulsory Revisions
  1/ In the discussion, please stress the fact and explain more detailed that it concerns a local process through which CRPS leads to macrovascular changes (i.e. no increase of CCA-IMT, gradient in the arm towards the hand).

  2/ Rephrase the abstracts conclusion to exclude “acute phase of CRPS” since the mean duration of symptoms was 16 months according to table 1. Formulate the conclusion in two sentences. In the first, state your conclusion drawn from the findings. In the second sentence, discuss these findings in relation to what is known from the literature.

  3/ Introduction, second paragraph: include a statement that IMT does not necessarily reflect pathological changing but is largely influenced by increasing age. This is important and should also be mentioned in the discussion, e.g. state whether the subgroups have different ages or not.

  4/ Materials and methods: section 2.1: this subparagraph needs to be rewritten since it is very unclear. Start with specifying how CRPS patients were included in the study, including how the diagnosis of CRPS was made and by whom (not
specified in the text at all). What is the number of patients initially studied. Next, what were exclusion criteria. How many patients were evaluated, and how many of these were not included after all (for instance the impossibility to complete the ultrasound examination due to pain). Then specify in a new paragraph how the control groups were included and evaluated (for the peripheral nerve injury group and lastly for the pain free controls). How was the diagnosis of peripheral nerve injury made (what EMG cut-off values, what clinical symptoms). The last sentence of this section raises a lot of questions: is only the dominant hand studied in the CRPS patients? If so, why is this? Is this also the case for the peripheral nerve injury group? Clearly state that the measurements were not blinded to clinical information as you specify in the discussion.

5/ Section 2.2.1: please specify measurement of the brachial and radial artery, which probe, which position, which position of the arm, etc.

6/ Please explain in discussion the difference in disease duration between CRPS and peripheral nerve injury patients since this may be a very important confounder.

7/ Follow the same order in the result section as outlined in the materials and method section: start with demographic data, next discuss CCA-IMT, next BA-IMT, RA-IMT, introduce Q-RA/CCA-IMT.

8/ Result section: mention all measured numbers in the text, so that the tables are not necessary to be read (they might even be abolished). For instance, section 3.2: “Mean brachial IMT (BRA-IMT) was significantly increased on the affected side only in CRPS patients compared to PFC (0.42 ± 0.06 vs. 0.40 ± 0.08; p-value…).

9/ Remove in section 3.2 and 3.3 the correlations between the arteries since its irrelevant to the present study and is largely caused by IMT influenced by effects such as age.

10/ Please explain why a subgroup analysis was made of the median nerve injury patients: remember that you have extremely small subgroups. The difference is more likely due to chance than it is a real observation. In addition, it is not used in the discussion and the minute difference between ulnar and median nerve patients approaches the technical limitations of ultrasonographic devices.

11/ Please specify the effect of disease duration on all of the parameters studied in all subgroups.

12/ Rewrite the conclusion since it is now too bold to fit the data. Make no such strong mention of the relation between inflammation and locally increased IMT in CRPS, since the study design is not capable of demonstrating such a correlation.

- Minor Essential Revisions

1/ Please remove the abbreviation CRPS from the title and specify that it
concerns type I.

2/ Rewrite the abstract to make it more readable (i.e. consistently use two decimal places; specify values according to artery, then patient group, then side; specify p-values).

3/ Introduction, second sentence: correct sings into signs.

4/ Introduction, tenth sentence: ...levels of proinflammatory... correct to pro-inflammatory.

5/ Section 2.2: please specify inter- and intra-observer agreement for the study sonographer compared to the experienced sonographer.

6/ Section 2.2.1: please make sure the IMT is normally distributed. If so, write this down. If not, use medians +/- interquartile range instead of mean +/- SD.

7/ Section 2.3: make sure that for all values there is a normal distribution before using means +/- SD and corresponding statistical tests. Why are the associations tested between quantitative values as stated in last sentence?

8/ Remove from discussion the sentences starting with “Myredal stated ...” to “atherosclerotic disease” since it is not relevant.

9/ In the discussion, the authors suggest that the findings are the result of both a systemic as well as a local inflammation process. Explain in more detail how the CCA is not influenced while the BA is only on the affected side.

10/ Table 1: correct the percentages of genders per subgroup; remove median and range if normal distribution, please explain how someone in the peripheral nerve injury group can have a maximal pain intensity of 1 while the current pain level is 2.

11/ Change the order of the legends of tables and figures accordingly: Values mean +/- SD. Percentages explained. P-values explained. Abbreviations explained. References to footnote (e.g. in table 1: multiple answers possible).

- Discretionary Revisions

1/ The authors might consider removing table 2 and 3 since most of the values have been specified in the text and figures 1-3.

2/ In the discussion, the authors could specify how they intend to do a more extensive study to elucidate the questions that the present study has arisen, e.g. longitudinal ultrasound follow-up starting early after symptoms of CRPS have started with simultaneously measurements of inflammatory markers. In addition, one could provide a hint of a new study confirming the finding of locally enlarged IMT in peripheral nerve injury patients.

**Level of interest:** An article of importance in its field
**Quality of written English:** Needs some language corrections before being published

**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.