Reviewer’s report

Title: Quality of life scores differs between genotypic groups of patients with suspected hereditary hemochromatosis

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Reviewer: Annick Vanclooster

Reviewer’s report:

Dear Editor,

Fonseca et al. wrote an interesting manuscript about the quality of life (QoL) in patients with hereditary haemochromatosis (HH). It is important that the QoL in patients with HH is studied, but I have some major methodological remarks about this article, that need to be addressed.

1. 79 patients with hyperferritinemia are included in this study of which 29 are homozygous for c.C282Y. Group 2 is a combination of patient with primary iron overload with or without HFE mutations. Patients with only one gene mutation as included in Group 2 in this study are carriers and do not have HH. Also patients without the presence of any HFE gene defect are included in group 2, although this is not the reason for their iron overload and so they are not HH patients. In Table 1, there is already a significant difference between group 1 and 2 in demographic data. You would expect there are more men than women if you have a mean age of 45 years, but there are far more men in group 2. The serum ferritin (SF) and transferrin saturation (TS) values differ significantly at time of inclusion. In principle, you need to have two groups with comparable demographic data, to allow meaningful statistical conclusions. In particular in this study, where the genotype is associated with QoL, there should be no statistical difference in ferritin. Is the perceived difference in QoL associated to the genotype, to the gender of the patients in each group, to the transferrin saturation? It is methodologically impossible to reach any conclusions on this matter. It would be meaningful to plot QoL against ferritin for both genetic groups into one pool. That way the researchers could at least get an indication whether the ferritin level correlates with QoL or not. The problem that then remains, is the absence of formal proof of iron accumulation (by biopsy or MRI). Hyperferritinemia can occur as a biochemical aberrancy in the absence of actual iron overload.

2. Although there are no significant differences between the two groups in the supplementary table, table 2 shows differences on four domains: physical functioning, bodily pain, vitality, social functioning. Since the groups are not comparable, the scores should be given graphically with rationale of the SF value and the different SF-36 items.

3. There is no information on medical data of the patients. Do they have diabetes, osteoporosis, liver failure, … All these items will probably decrease the QoL and are more likely in c.C282Y homozygous patients.
4. The SF-36 questionnaire was filled in after knowledge of the genotype (p6). Patients were treated already with phlebotomies? Literature describes patients benefit from treatment, which can influence the outcome of the SF-36 questionnaire. What about the 'additional question' that was asked to evaluate the transition of health status within a year.

Kind regards,

Annick

Nurse Specialist Metabolic Diseases and haemochromatosis, RN, PhD

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
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No

Are the conclusions drawn adequately supported by the data shown?
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