Reviewer’s report

Title: Quality of Life (QoL) assessment in a cohort of Phenylketonuria patients

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Reviewer: Annet A Bosch

Reviewer’s report:

Quality of life is an important outcome in PKU and the authors address an important issue in PKU at this time. Besides the quality of life, the authors importantly evaluated depression and anxiety in the patients, with the highly relevant outcome that no consistent abnormalities were detected. However, some issues need to be discussed.

Also, the use of English needs attention.

Background

Minor essential revisions:

The protein restricted diet does indeed require much effort but there is no evidence that it takes more effort in adulthood. Most adults relax their diet somewhat, partly due to higher advised Phe ranges, and partly because risks of high phe levels are not as clear as in childhood. Please correct.

The authors state that WHOQoL-100 and Pedsqol are better devised questionnaires for PKU than previously used instruments, and that this is the first study to use Pedsqol.

1. However, the study referred to in this manuscript (Demirdas et al) specifically has used Pedsqol as well and compared BH4 responsive to not responsive patients, both before and after start of the BH4 treatment.

2. There is no evidence that PedsQL and WHOQoL-100 are better devised for PKU than other questionnaires. Please report why the authors think this is the case.

Materials and Methods

Major compulsory revisions:

1. Patient selection is somewhat unclear:

A total of 43 patients has participated in the study. Please report how many patients had been invited to participate, what the response rate was, how many patients had to be excluded due to missing data.

2. The definition of Mild PKU is not clear:

“Phe blood level ranging from 600-1200”. Is the the Phe value at the time of newborn screening? That would indeed be a sound criterium for mild disease. Another commonly used criterium for mild disease is protein tolerance. Protein
tolerance is not reported in this manuscript but would be highly valuable. Comparing protein tolerance of the mild/BH4 versus the diet only group would provide much more insight into both groups. Please provide.

3. The authors report mild BH4 responsive patients, and classical patients not treated with BH4.

Were all mild BH4 treated patients also mild before the start of BH4? Classical patients can be BH4 responsive as well, have all classical patients been tested for responsiveness? How clear is it that the BH4 treatment itself causes the better QoL, is it also possible that the mild vs severe causes the better QoL?

4. Patients from age 6 and up have completed the PedsQL. However, generally patients aged under 9 are not able to complete the PedsQL by themselves because of yet insufficient reading skills. How have the authors ensured patients age 6-7 have completed the questionnaires by themselves?

5. The multivariate linear regression model evaluates treatment length in months. It is unclear what is the definition of treatment length. Is it simply the time patients have been treated? As all patients have been diagnosed in the newborn period, is it simply age?

Results

Major compulsory revisions:

1. Table 1: only total scores of QoL measurements are reported. Please provide domains and scores in a table together with norm scores.

2. Table 2: does not provide extra insights

3. The authors state that phe tolerance increased 2-4 times following BH4 treatment.

For this they refer to a case series of 6 USA patients. Please report data on phe tolerance or protein tolerance for the patients participating in this study.

4. Authors report that proxy QoL scores (pedsqol) were comparable to healthy children.

Please report data and control group data.

5. Authors report that QoL scores were significantly higher for mild PKU/BH4 compared to classical PKU. It is unclear if this is the child report or parental report, please specify.

6. Line 272:

Authors state that: In adult patients QoL was also significantly lower in males (RC=-2.58; 95%CI: -4.44; -0.72) as compared to females and in those with postgraduate education (RC=3.26; 95%CI: 1.33; 5.18) as compared to patients with secondary school education (reference).

This is not correct as the RC is 3.26 Please correct.

7. Discussion: much of the discussion addresses the SF36 questionnaire, which
has not been used in this study, nor in some of the studies the authors refer to. This paragraph may be shortened.

8. Authors report that increased duration of treatment improved QoL significantly. The question is what the clinical meaning is, with an increase of 0.03 per months of treatment length. First: do the author think this will make a clinical difference? Second: All patients have been diagnosed in the first weeks of life, does this imply that increasing age gives a higher QoL? Or do authors imply that treatment improves the QoL of a 10 year old compared to a 6 year old, even if both have been on diet since infancy?

9. TAD, BDI and STAI-Y
An important finding of this study is that no consistent abnormalities have been found on these questionnaires. As this is the first report of these questionnaires in these patients this is an important finding and should be stressed more.

Discussion
Major compulsory revisons:
1. The authors state that:
“This finding seems to suggest that whatever treatment (diet or BH4) is effective in improving QoL of PKU patients in the long run.”

As commented above the question is whether an improvement of 0.03 per month is clinically relevant at all. Also, PKU treatment is preventive (preventing damage due to high Phe values) and there is no reason why a younger (shorter reated ) patient would have a lower QoL which can be improved by treatment of longer duration. Please explain and rephrase.

2 . “Diet remains the mainstay for patients with classical disease, whereas those affected by mild PKU and struggling to comply with the diet regimen have the opportunity to rely on BH4 medical treatment.”

The opportunity to benefit from BH4 is not only in mild patients, but severe patients may be responsive as well, and not all mild patients may be responsive, please rephrase.

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

Quality of written English:Needs some language corrections before being published

Statistical review:Yes, but I do not feel adequately qualified to assess the statistics.

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