Author’s response to reviews

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

Authors:

Chiara Cazzorla (chiara.cazzorla@sanita.padova.it)
Luca Cegolon (l.cegolon@gmail.com)
Alessandro P Burlina (Alessandro.Burlina@aslbassano.it)
Andrea Celato (andrea.celato@uniroma1.it)
Massa Pamela (massa_pamela@yahoo.it)
Laura Giordano (laura.giordano.81@alice.it)
Giulia Polo (giulia.polo@gmail.com)
Aurora Daniele (aurora.daniele@unina2.it)
Francesco Salvatore (salvator@unina.it)
Alberto B Burlina (alberto.burlina@unipd.it)

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Author’s response to reviews: see over
To: Editorial board of BMC Public Health Journal

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I am resubmitting a revised version of the manuscript entitled “Quality of Life (QoL) assessment in a cohort of Phenylketonuria patients”. We are very grateful to the editorial staff which have allowed us to improve our manuscript. We have taken into account all of your comments and we propose a new revised manuscript. Please find below “point by point” responses to your suggestions and questions.
We believe that the paper has been significantly revised, largely due to the reviewers’ thoughtful comments.

All authors have reviewed and approved the manuscript.

As the author responsible for correspondence, as well as for communications among authors with regard to revisions and approval of proofs, I appreciate the Journal’s consideration and welcome comments.

Sincerely yours,

Alberto Burlina
Director
Division of Inherited Metabolic Diseases
Department of Pediatrics
University Hospital
Via Giustiniani 3
35128 Padova Italy
Responses to referee’s comments:

REVIEWER: Nicola Longo

Critique 1.: Line 118: Current guidelines do not restrict BH4 use. A trial is actually recommended in all patients with PKU. Patients with milder forms of PKU are more likely to respond to BH4 treatments

Authors’ response to critique 1.: Line118: We have rewritten the entire sentence as follows: “Current guidelines suggest that a trial with sapropterin can be provided to all PKU patients [13], nevertheless patients with milder forms of the disease are more likely to benefit of BH4 treatment rather than classical ones.”

Critique 2.: Table 1: please add the control value for QOL in unaffected people with relative reference

Authors’ response to critique 2.: Table 1: We added the control values of QoL of both groups (pediatric and adult patients) and we added the relative reference to the bibliography.

Critique 3.: Table 2: please make the average ± SD of concomitant phe values and mean phe values and comment in the text on whether the values differ statistically among groups

Authors’ response to critique 3.: We added mean + SD phe values at assessment in both groups and commented results in the text as follows: “An ANOVA test was run to compare the mean Phe values of each group (mild PKU patients on BH4 vs. classical PKU patients on diet) with mild PKU patients on BH4, showing significantly lower mean Phe blood values and narrower SD (see table 2c)”

Critique 4.: Unclear what was actually done in table 3 and 4. Was a regression performed between values of behavioral testing and the different variables? What are the variables (age, school, treatment length, BH4)? Was linear regression done for each variable and then combined with other variables? Which one were the combinations used in the multivariate analysis?

Authors’ response to critique 4.: A multivariable linear regression model was fitted to investigate the simultaneous effect of the different covariates on QoL. The linear regression reports the association between each predictor and the outcome after holding constant the effect of all other covariates included in the model.

Critique 5.: Was there any correlation of scores with average Phe levels in groups?

Authors’ response to critique 5.: We added a table (table 5), which report the association between Phe levels (both at assessment and during the course of the previous twelve months) and QoL scores in both groups.
Critique 6.:
It seems that in some cases a group comparison was used (males), but it is unclear what was the comparison group (was this the normal controls?).

Authors’ response to critique 6.:
We clarified throughout the test that for “controls” were intended QoL tests normative data and not an healthy control group and we added normative data and related references. Males were compared with females (reference group of the multivariable regression models).

Critique 7.:
The tables need to be corrected to clarify the points above and the text corrected accordingly.

Authors’ response to critique 7.:
We have corrected the tables and the text to clarify the point as suggested.
REVIEWER: Annet A Bosch

Background
Minor essential revisions:

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.

Authors’ response:
The sentence has been rewritten as follows “Diet should be maintained lifelong and this requires a lot of effort, especially during adulthood owing to the growing instances of social relationships”. The “efforts” we referred to, were the ones concerning the growing opportunities of social instances and not to a different burden of diet managing during adulthood.

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.

Specific comment 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 patents, both before and after start of the BH4 treatment.

Authors’ response to specific comment 1:
We clarified that we used up to date instruments to assess QoL, in order to assess if those instruments better outline possible differences compared to previous inventories. Indeed it is true that no previous articles focused on revealing an advantage using this instruments in evaluating, for instances, PKU patients but we argumented about possible advantages of WHOQOL-100 as compared to SF-36 model inventories.

Specific comment 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.

Authors’ response to specific comment 2:
It’s indeed true that no articles stated an advantage in PKU patients QoL assessment, using PedsQoL or WHOQOL-100. In the text we argued about possible strenghts:
- expanded numbers of questions
- better definition of the different dimensions which constitute QoL construct
- reformulation of some questions that seems to better fit to a chronic disorder
- better assessment of non medical instances and limitations
This truly represent a field which need further studies.

Materials and Methods
Major compulsory revision
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.

**Authors’ response to specific comment 1:**
The sentence has been rewritten as follows: “A total of 30 mild BH₄ respondent patients have been selected to participate to the study. 3 of them were excluded due age criteria (patients under 4 years of age), 2 were excluded due to the presence of mental impairment and 3 did not give their consent to participate to the study. An almost identical number of classical PKU patients were then recruited considering gender, disease severity and age-matching criteria”

**Specific comment 2.**
The definition of Mild PKU is not clear: “Phe blood level ranging from 600-1200”. Is 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

**Authors’ response to specific comment 2:**
The classification of the patients (classical vs. mild) was based upon the phe value at the time of newborn screening. Moreover we used also Phe tolerance referring to a previous article in which patients involved in the present study were biochemically studied. Finally molecular genetic testing provided further information about genotype-phenotype correlation and BH₄ responsiveness.

**Specific comment 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?

**Authors’ response to specific comment 3:**
Mild PKU patients were assessed for Phe levels before the treatment, Phe tolerance and genotype analysis. Not all the classical PKU patients were tested for BH₄ responsiveness, and BH₄ loading test was performed only in classical PKU patients whose genotype were supposed to be respondent to BH₄. None of the classical patients tested demonstrated a reduction of Phe levels as recommended for BH₄ loading test assessment [Anjema, K., van Rijn, M., Hofstede, F.C., Bosch, A.M., Hollak, C.E., Rubio-Gozalbo, E., et al. (2013). Tetrahydrobiopterin responsiveness in phenylketonuria: prediction with the 48-hour loading test and genotype. *Orphanet J Rare Dis*, 8(1),103]. In terms of QoL assessment in the two group of patients, we largely discussed in the text the limitations of the study design, not allowing to establish if better QoL has to be referred to the severity of the disease or to the treatment options. All the sentences, in which this issue could be misleading, were corrected.

**Specific comment 4.**
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?

**Authors’ response to specific comment 4:**
We cleared up in the text that indeed in children 6-7 years old of age PedsQoL was administered by an interviewer and the dedicated version of the instrument (5-7 years age) was used.

**Specific comment 5.**
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?

**Authors’ response to specific comment 5:**
Treatment length is the duration of current treatment type

**Results**
**Major compulsory revision**

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

**Authors’ response to specific comment 1:**
This represents a preliminary study concerning QoL in PKU patients. Actually the statistics of different dimensions that QoL inventories imply would need further statistical dissertation and analysis. The reliability of the different dimensions that constitute the QoL construct will be investigated in a future study.

**Specific comment 2.**
Table 2: does not provide extra insights

**Authors’ response to specific comment 2**
Table 2 report Phe levels at the time of assessment and mean Phe values over the course of the previous twelve months that have now been compared in the two group of patients (mild PKU on BH₄ treatment and classical ones on diet).

**Specific comment 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.

**Authors’ response to specific comment 3:**
There was a typing error of the reference voice and the sentence refer to the article that was the 21th on bibliography (for instance: Burlina A, Blau N: *Effect of BH₄ supplementation on phenylalanine tolerance. J Inherit Metab Dis* 2009, 32:40-45.), in which were involved the patients who have been enrolled in the present study.

**Specific comment 4:**
4. Authors report that proxy QoL scores (pedsqol) were comparable to healthy children. Please report data and control group data.
Authors’ response to specific comment 4:
We have added the control value for QoL both for children and parents and we added the relative reference to the bibliography.

Specific comment 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.

Authors’ response to specific comment 5:
This refers to child report. Parental report were only analysed and compared to child report. We clarified this issue in the text.

Specific comment 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 272 (reference) and in those with postgraduate education (RC=3.26; 95%CI: 1.33; 5.18) as compared to 273 patients with secondary school education (reference). This is not correct as the RC is 3.26 Please correct.

Authors’ response to specific comment 6:
There was a typo error: QoL was indeed “higher” in those with higher educational level. The body text has been now amended accordingly.

Comment 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.

Authors’ response to specific comment 7:
In the discussion section we considered previous instruments as SF-36 inventory, an instrument that encompasses objective measures in addition to perceived state. The aim was to suggest possible strengths of the instruments we used in this study compared to SF-36. Anyhow we tried to shorten the text on this field to make it more readable.

Specific comment 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?

Authors’ response to specific comment 8:
0.03 is the numeric estimate of QoL enhancement per unit increase of current treatment length. Increasing treatment time (and so also age) may signify better compliance with diet or pharmacological therapy.

Specific comment 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.

Authors’ response to specific comment 9:
We briefly discussed the issue concerning psychiatric and psychological functioning in PKU patients as suggested. Owing to the focus of the article psychiatric aspects can not be fully deepened and will be detailed in a future research.

Discussion
Major compulsory revisons:
Specific Comment 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 treated) patient would have a lower QoL which can be improved by treatment of longer duration. Please explain and rephrase.

Authors’ response to specific comment 1:
Please see comment above. It may be the case that treatment compliance improves over time (irrespective of treatment type: diet or BH4).

Specific comment 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.

Authors’ response to specific comment 2:
We clarified in the text that BH4 represent an option also in classical PKU patients, although diet remains the mainstay in classical ones.

IN ADDITION

(1) Competing Interests: we moved the Competing Interests section after the Conclusion and before the Authors’ contributions.

(2) Authors' contributions: we included an Author’s contributions section before the Acknowledgements and Reference list. For the author's contribution we followed your suggestions. All the contributors who do not meet the criteria for authorship are listed in the acknowledgements section.

(3) We correct the spelling of “Phenilketonuria”.