Revisor A 🡪 The modifications are represented in green along the main document, as well as the answers in this document.

Review of the manuscript #11837-42232-1

RELEVANCE: The issue is extremely important in Paediatric Neurology. It will help increase physicians awareness about the efficacy and safety of ketogenic diet (KD). It may improve national practice as it may help increase acceptance of KD as an earlier option in refractory epilepsy escalation of treatment.

ORIGINALITY: There are few data published on efficacy and safety of KD in children at a national level. The study focus on the efficacy of KD beyond seizure control, as it also shares data on behaviour and alertness improvement.

MISCONDUCT: None that I am aware of.

 The authors are grateful for the attention of the reviewer!

STRUCTURE OF THE MANUSCRIPT

Title: It is instructive and it does summarize the manuscript.

Abstract: It reflects the contents of the manuscript and it is well structured, although it needs to be re-written.

The abstract should be consistent with the text. In the results section of the main manuscript efficacy is reported for the 29 patients who completed more than 3 months on KD, and also for the subgroup who completed 24 months on KD. In the abstract section, results on efficacy are shown only for the ten patients who completed 24 months on KD. In the abstract, results should be presented for the general sample of the study, not for subgroups.

I would also suggest rewriting the abstract after revising the main text as suggested below.

In the abstract section, please show age distribution as median (25th percentile – 75th percentile). I would also suggest to include a new paragraph with the heading “Aims” and separate that from the “introduction” paragraph. 🡪 We made the modifications suggested by the reviewer.

Introduction: The objectives are clearly described and it explains the relevance of the study.

 Thank you.

Methods, Results, Figures, and Tables:

Although the issue is extremely relevant, two major concerns regarding study design compromise the quality of the manuscript on its current form.

Please find below my two major concerns (#1 and #2) and some minor suggestions (#3):

#1

My main concern regarding the study design is the definition of the study sample.

I do not agree with the inclusion of two patients in duplicates. These patients should have been included just once, considering their first time on KD.

It is also weird to be excluding patients along the way. Please define which is the main outcome of your study and pick the patients evaluated for that as your sample.

If you decide you are able to evaluate efficacy only in patients who completed more than 3 months of KD, please include “less than 3 months of KD” as an exclusion criteria.

If efficacy in patients who completed at least 3 months of KD is the main outcome of your study, having evaluated efficacy in 29 patients, your total study sample should have been this 29 patients. It is obvious you will have a smaller number of patients who were genetically tested – and that’s fine, because that’s not your main outcome.

I would suggest to rewrite your results saying you had xx eligible patients, xx were excluded due to x (n=?), y (n=?), and z (n=?). And then keep that number of patients as your sample. For consistency, please rewrite the demographics section (age and sex distributions) for your final sample of 29 patients.

In summary, decide your sample first, describing how many patients were eligible and how many patients were excluded and why. Then, describe the demographics of that sample. Then, present the outcomes for that sample (you will have no missing patients for your main outcome of interest – seizure control, but you may have missing patients for the other outcomes and that’s fine). 🡪 We clarified this question, selecting our sample, in this case the 29 patients (we added a figure representing the exclusion of the other patients). With better definition of the inclusion and exclusion criteria, these 29 represent only one pair of patient& diet.

#2

For a relatively rare therapeutic option, it is natural to have a sample size of 20 or so - that’s fine. Results are thus descriptive and that’s also appropriate for a study like this. Despite that, please be aware you should not present relative frequencies as % having such a small sample size, just keep the absolute frequencies (n). If appropriate, please show the numerator and the denominator. Whenever you present results for a particular outcome, which is not the main outcome of the study, and the number of patients evaluated for that outcome is smaller than your total sample size, you should show the number of observations and the number of patients evaluated for that outcome. In other words, show the absolute frequency of that outcome and also the denominator or number of patients evaluated for that outcome, such as x/y. 🡪 We changed the numbers representation as suggested by the revisor.

#3

Other minor suggestions to be considered:

• Instead of “Statistical analysis was performed with the 14.2 version of the STATA software (Copyright 1985-2015 StataCorp LP)” consider “Descriptive analysis was performed using the 14.2 version of the STATA software (Copyright 1985-2015 StataCorp LP)” 🡪 We changed as suggested by the revisor.

• Do not use the term “significant” for reasons other than statistical significance. In the methods section instead of “We defined efficacy in seizure control as A a seizure reduction rate ≥of 50% was significant; or higher.” use “We defined efficacy in seizure control as a seizure reduction rate of 50% or higher.” 🡪 We changed as suggested by the revisor.

 • In the results section, it should be stated that there were 36 pairs patient-diet corresponding to a total of 34 patients, not 36 patients as it is said. 🡪 With the new definition of the group, this disappears.

• Age distribution should have been shown in median and interquartile range using the same number of decimals for each value (e.g., 0.8 to 19.0 years). Interquartile range is usually shown as “x years – y years” representing the limits of the interquartile range (25th percentile – 75th percentile), not as the absolute difference between the 75th percentile and the 25th percentile. 🡪 We changed as suggested by the revisor.

• In the fourth paragraph of the results section it is said that “For the twenty-five group, the median duration of the KD was 14.9 months (minimum 1.2 – maximum 36.1 months; IQR 21.6)”. The sentence is incomplete. Does the “twenty-five group” refer to the 25 patients who completed the first month on KD? 🡪 With the new definition of the group, this disappears.

• Age categories shown in Figure 1 are unequal. Is there a biological rationale for this? If there is, please explain it. If there isn’t, please consider redoing the categorization of age into categories with equal size. 🡪 We changed as suggested by the revisor.

• In table 1, the counting looks inaccurate. Looks like there are 3 missing in the section “LennoxGastaut syndrome” and 2 missing in the section “Ohthara syndrome”. 🡪 We changed as suggested by the revisor.

• Instead of “In short, there was ≥50% seizure reduction in 58.6% of the patients.” consider writing “In short, there was ≥50% seizure reduction in seventeen patients.” 🡪 We changed as suggested by the revisor.

• In the fifth paragraph of the “efficacy assessment” results section sounds like you are discussing the results. In the results section, please avoid subjective comments like “Meanwhile the results were not so satisfactory for West syndrome patients regarding seizures improvement” – keep that for the discussion section. In the results section, you may say “Meanwhile, efficacy in seizure control was lower in the West syndrome group.” 🡪 We changed as suggested by the revisor.

• I would rather classify the improvement in behaviour and alertness as: “marked”; “moderate”; “none”. Personally, I would avoid “substantial” for making it clear that is different from “significant”. 🡪 We changed as suggested by the revisor.

• Please invert the layout of table 2 so that it looks cleaner, as shown below. 🡪 We changed as suggested by the revisor.

In table 2 and 3 please consider changing the labelling of the outcomes to: “Seizure control”; “Improved awareness”; “Improved behaviour”. Also consider changing A, B, and C to “marked”, “moderate”, and “none”. 🡪 We changed as suggested by the revisor.

• The relative frequency or percentages presented in the tables are useless considering the small number of subjects studied. Show the absolute frequencies only. 🡪 We changed as suggested by the revisor.

• Table 3 adds no relevant information to the text. Please delete it or at least convert the layout into something cleaner, such as: 🡪 We changed as suggested by the revisor.

In your results section, after showing the results for the entire sample, you also show the results for a smaller group of patients who completed a longer period on KD. Although that’s appropriate, why do you look at a subgroup of patients who completed 18 months or more on KD in the third paragraph of the “efficacy assessment” section and then, in the tenth paragraph of the “efficacy assessment” section, you look at another subgroup of patients who completed 24 month of KD or more. Please pick one time frame – either 18 months or 24 months - or show results for both subgroups each time. Please note that in the section “demographics” you have shown the retention rates at 12 months and 18 months, but not at 24 months. 🡪 We changed as suggested by the revisor.

• Please consider moving the first sentence in the section “secondary effects” of the results, which is interpretative, into the respective section of the discussion. 🡪 We changed as suggested by the revisor.

Discussion: It explains the relevance of the results. It acknowledges that the main limitation is the small sample size. It also describes areas that need further study.

In the discussion section consider changing the sentence “Due to the limited dimension of our cohort, we cannot draw conclusions on efficacy related to seizure reduction. However, we observed an important improvement in what concerns alertness and behaviour, as previously described by other authors.” to “Our small sample size limits our ability to assess efficacy. Despite that, our results suggest that KD may improve not only seizure control, but also alertness and behaviour, as previously described by other authors.” 🡪 We changed as suggested by the revisor.

Conclusions: It reinforces the main take-home message.

Although it is important to stress the need to change practices so that KD is better accepted by children and their families, the last sentence is not based on the results of this study. As a result, I would suggest changing “This retrospective study made us aware of” to “We would also like to stress that…”. 🡪 We changed as suggested by the revisor.

References: The literature review is considered adequately and it follows AMP’s style.

Tables / Figures: Please see comments above.

Acknowledgments: Adequate.

EXTENSION: In general, the extension is adequate.

PRESENTATION: The manuscript is clearly and logically presented if it is revised to account for the already mentioned main concerns regarding study design and presentation of results.

RECOMMENDATION REGARDING PUBLICATION: It should be considered for publication after major revision.

Thanks for the very detailed analysis and precious suggestions!