Author's response to reviews

Title: Quality of life in childhood epilepsy with lateralized focus

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Author's response to reviews: see over
Dear Dr. Alam,

we send you the corrected manuscript "Quality of life in childhood epilepsy with lateralized epileptogenic foci" by Mathiak et al. We considered all the comments of the reviewers and we made substantial revisions and improvements to the manuscript. Moreover a native English speaker checked for the use of language. We are confident that the revision substantially improved the quality and clarity of the manuscript and we hope that it can be accepted for publication in *BMC Neurology*.

Sincerely yours,

[Signature]

Krystyna Mathiak
The reply to the first reviewer, Dr. Nathalie Jette:

1. First of all, the manuscript needs to be edited for language, as there are numerous grammatical errors throughout the manuscript. I began making note of these but by the end of the background section, I had already found numerous English grammatical errors. For example, the title should read “Quality of life in childhood epilepsy with a lateralized potentially epileptogenic focus” or “Quality of life in childhood epilepsy with lateralized epileptogenic foci”. Focus is frequently used instead of foci. Words are often omitted, etc. For example on page 2 (abstract) the first sentence of the results should read: “We found a significant correlation between foci lateralization and reduced QOL…” The first sentence of the conclusion (abstract) should read: “…and right-hemispheric foci are associated with discordant QOL scores” for example.

We rephrased all the sentences pointed out by the reviewer according to her advice. Moreover, following the suggestion of the reviewer, a native English speaker, Dr. Mara Sittampalam (a medical doctor, Neurology Registrar, UK), revised the manuscript thoroughly.

2. They should not use the word “impact” in the first sentence of the conclusion as this assumes causation. All they can say is that there is an association between the hemispheric localization of the epileptiform discharges and QOL scores.

We rephrased the conclusions section of the abstract as suggested by the reviewer.

3. The last sentence of the abstract needs to be deleted (unclear) and a clear aim or objective sentence added. “The objective of our study was to …”

We rephrased the last sentence of the abstract as suggested by the reviewer.

4. In the first sentence of the methods (abstract) the authors need to clarify which QOL questionnaire they administered.

We rephrased the methods section of the abstract as suggested by the reviewer, providing the full name of the scale.

5. Background should be shortened by at least ½ page. It is too detailed for an introduction. The authors could consider moving some of the information, which is clearly interesting, to the discussion.

Following suggestion of the reviewer, in the revised manuscript we shortened the 2nd and the 5th paragraph of introduction, moving part of the information to the discussion.

6. Background, last sentence of third paragraph should say: “Studying behavioural consequences of lateralized potentially epileptogenic foci may offer some insight into …” I am concerned that the authors are using the terminology “lateralized seizures” when all they did is an EEG and the seizures were never captured in a seizure monitoring unit. Thus all they can say is that the patients had “lateralized epileptiform discharges” (unless they captured seizures on all EEGs which does not appear to be the case).

According to the reviewer’s suggestion, we rephrased the third paragraph of the background section and adapted the terminology throughout the manuscript.

7. In the background, the objective of the study needs to be stated. Currently the authors say: “We wanted to apply QOLCE as an epilepsy specific measure for subjective wellbeing in children with unilateral epilepsy”. The objective is not clear. Again I do not believe the seizures were captured on video EEG (only epileptiform discharges were). I would suggest an objective such as: Our objective was to assess whether there was an association between lateralized epileptiform discharges in childhood epilepsy and QOL.

We stated the objective of the study as proposed by the reviewer.

8. Methods: The authors state that one of the exclusion was “anatomical malformations detected by magnetic resonance or computed tomography”. Yet only 23/31 children had neuro-imaging. This is a major limitation of the study. All children should have had neuro-imaging. What if they had bilateral lesions on neuro-imaging? Or what if some of them had a lesion that was contralateral to the EEG focus?

All the children underwent neurological and neuropsychological examination and were under extensive clinical care. Our group encompassed also children with benign rolandic
epilepsy, who were not referred to brain imaging by their neurologist. According to the
guidelines of ILAE (Gaillard, 2009), any patient with partial epilepsy should have
neuroimaging examination performed, unless we deal with clinical-EEG picture of benign
rolandic epilepsy (benign partial epilepsy with centro-temporal spikes). Based on clinical-
EEG information, we expected no anatomical malformations in those 8 subjects who
underwent no brain imaging. However, we cannot exclude it with certainty. The
consequences of bilateral or contralateral lesions – that were not detected in the
neuroimaging or not diagnosed due to a lack of clinical signs – would be a reduced power
of the study, just like undetected contralateral foci. Therefore it can well be that the effect
size was underestimated. This problem is further addressed in the discussion. We thank
the reviewer for pointing out this limitation.

9. The authors need to clarify if handedness was assessed. I apologize to the author if it was assessed, but I
cannot see this data in the manuscript. This is a critical piece of information, as hemispheric dominance is
more important than simply “side” e.g right or left side. This needs to be addressed by the authors.

We agree with the reviewer that hemispheric dominance is an important factor in studies
on functional lateralization. We decided not to assess the handedness of our subjects.
While the relationship between handedness and hemispheric dominance for language
appears to be strong in healthy right-handers (over 95%), it is much harder to draw any
conclusions in left-handed or ambidextrous subjects. Over 60% of healthy left-handers
have left hemisphere dominant for language (Hellige, 1990; Medina et al., 2007) and this
pattern of hemispheric variability is characteristic also for other cognitive functions (Hellige,
1990). Therefore, in studies of healthy subjects it is reasonable to include only left-handers
or to control for handedness. Hemispheric dominance is however to a much lower extent
correlated with handedness in epilepsy, both in right- and left-handers (Medina et al.,
2007). Consequently, a formal assessment of handedness in our youngest patients would
stretch the time of examination and affect the results of other scales, while adding no
reliable information on hemispheric dominance for cognitive and emotional functions that
were of interest to us. Moreover, the exclusion of left-handed subjects may have led to
lower number of subjects and a lower generalizability. To control reliably for hemispheric
dominance we would need to apply invasive (e.g. Wada testing) or technically demanding
and expensive (fMRI) techniques that were out of the scope of our study.

If some of our subjects would have a reversed hemispheric dominance pattern, this would
result in decrease of a statistical power of our results. It limits, therefore, conclusions
concerning negative findings of our study. We agree with the reviewer that this is an
important issue to address and we discuss it in the limitations section.

Minor Essential Revisions
1. EEG should be spelled in full in abstract (as the abbreviation has not previously been defined)
2. Should not use abbreviations at the beginning of a sentence – need to spell in full (e.g. page 3 “WHO” and
“QOL” are used at the beginning of sentences; WHO was never defined before in the text).
3. References are usually numbers as “[8]” but at times the authors write “[see: 4]”. It is unclear to me why
they used both these formats.
4. Second sentence of background should read: “…affecting 3.6 to 4.2 per 1000 children…”
5. Second paragraph of background should read: “demonstrated in a study of 504 children”
6. Second paragraph of background should read: “It was observed that mood is the strongest predictor…”
7. I stopped writing down grammatical errors after page 3 as there were too many. The manuscript needs to
be edited extensively grammatically.
8. The authors need to be consistent with their use of abbreviations. For example on page 8, They sometimes
use QOL (second line) and then on the next linewrite quality of life.

We considered all the above comments of the reviewer and we made corrections as
suggested.
The reply to the second reviewer, Dr. Mary Connolly:

The subject of quality of life in children with lateralized focus is of great interest to those who care for children with epilepsy. However, the number of subjects (31) in this study is very small. The criteria used to lateralize the focus according to the methods section is based on interictal epileptiform discharges. However, in clinical practice individuals with unilateral temporal lobe epilepsy may have bilateral interictal epileptiform discharges and also generalized spike and wave, the latter may be present on a genetic basis. The authors do not indicate if intensive video-EEG monitoring was performed which would confirm lateralization and localization of the ictal onset zone. If data on video-EEG monitoring are available, they should be added. Exclusion of children with structural lesions in the temporal lobes is also difficult to understand as seizures commonly arise in the same temporal lobe. Exclusion of children with bilateral mesial temporal lobe sclerosis would be appropriate. The quality of life tool used was appropriate but the conclusions which the authors draw are highly dependent on correct lateralization and localization of the ictal onset zone. In conclusion, the number of subjects in the study and the criteria used for lateralization limit the inferences which may be drawn from this study. Study of a larger number of subjects and clear criteria on how the ictal onset zone was determined such as video-EEG data would add greatly to this study.

The number of subjects in our study is a limiting factor. It limits in particular the interpretation of negative findings (e.g. lack of difference as concerns depression) and additionally, the statistical power does not allow for an assessment of lobar localization, which could provide a better insight in the neurobiological background of the observed disturbance. However, despite a limited number of subjects, we obtained statistically significant differences between the groups. Moreover, as compared to other studies applying equally strict criteria, we examined a relatively large group of 31 subjects fulfilling strict criteria of unilateral seizures and no structural lesions. The previous studies encompassed 12-23 children each (Cohen et al., 1990; Metz-Lutz et al., 1999; Kolk et al., 2001; Bedoin et al., 2006). We address this limitation in revised discussion.

Video-EEG monitoring was performed in a few patients, yet the seizures were not captured. However, based on interictal EEG, only patients with unilateral epileptiform discharges and without left-right side alternation on serial EEGs were included in that study. We agree with the reviewer that it would be of an advantage to apply intensive video-EEG monitoring. Also other diagnostic techniques, improving the precise focus lateralization, such as additional MEG or fMRI examination, were shown to be a very valuable addition. None of those methods, however, was used as a routine in research on epilepsy and they were not in the scope of our present study. A number of studies used interictal epileptiform discharges as a base to assess foci lateralization (e.g. Caplan et al., 2004; Bedoin et al., 2006). We discussed those options in a revised version of our manuscript, proposing combining all the above methods in future studies on focus lateralization, to partly overcome the problem of a small group size and give better insight into understanding of the underlying pathologies.

As pointed out by the reviewer, there is a broad variety of exclusion criteria applied among the studies on epilepsy. Children with structural lesions (that is, with symptomatic epilepsy) were excluded from our study in order to create the most possible homogeneous group with cryptogenic/idiopathic etiology of epilepsy. Any organic lesion might influence per se results of the study. Indeed, exclusion of children with structural lesions was applied in many previous studies; e.g. Caplan et al. (2004) excluded all children with an “MRI or CT evidence of brain abnormality other than hippocampal sclerosis”.

We agree with the reviewer as concerns the limitations of our study that she pointed out. In revised version of the manuscript we extended the discussion in order to address the mentioned problems.