Author's response to reviews

Title: Cognitive deficits following exposure to Pneumococcal Meningitis: An Event-Related Potential study

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Author's response to reviews: see over
Dear Editor-in-chief,

REF: MS: 4475451785222504 - Cognitive deficits following exposure to Pneumococcal Meningitis: An Event-Related Potential study

We are grateful to receive reviewer’s comments on our manuscript on the use of event-related potentials in determining the effects of pneumococcal meningitis on the cognitive outcomes of exposed children. We appreciate the positive sentiments forwarded by the reviewers and have taken careful consideration of the comments made and responded to each in a point-by-point format.

Many thanks,
Mike Kihara

Responses to Reviewer’s comments

1. As shown in other meningitis studies in Africa, a relatively high rate of HIV positive patients is reported. How was the percentage of HIV positive children in the study and control population?

   Reporting of HIV status of children admitted to the Kilifi District Hospital became part of normal management in 2008. The present study was carried out on children who had been admitted between 1994 and 2004 and as such, we do not have their HIV statuses. We have included a paragraph in the discussion on page 14 stating this fact.

2. General comments: In this paper auditory testing (Cortical Auditory Evoked Potentials) is used as a means to investigate cognitive deficits following PM. Although an audiological test was used the paper lacks information about the auditory functioning of the subjects. The reviewers advise to consult an audiologist for revision of the paper.

   We acknowledge that we have not tested for hearing loss per se but rather used the Kamplex audiometer® for screening the children’s better ear thresholds. We have however used peak-to-peak analysis of the N2
component so that its latency/amplitudes are independent of the P1, which would easily be affected in children with hearing impairments. A clearer discussion of this analysis has been included in paragraph 1 on page 9 of the revised manuscript.

3. Hearing loss is specified as “unable to hear 81 – 105dB on better ear”. This is not an adequate description of hearing loss. Hearing loss should be specified as a loss (in dB) or as a hearing threshold (in dB HL). Specify test frequencies or use a Pure Tone Average (PTA, e.g. 500, 1000, 2000 or 1000, 2000, 4000 Hz).

We have revised the manuscript and written a clearer account of the methodology as advised by the reviewer. This revision is on paragraph 2 on page 5 of the revised manuscript.

4. Please specify in more detail the hearing thresholds of the remaining 58 subjects (after excluding subjects with severe and profound hearing loss), specify at least average and SD hearing loss.

We used a screening test and so cannot report average hearing loss. The hearing thresholds were obtained in a sound-attenuated room where the ERPs are recorded but this does not meet the strict criteria of measuring hearing and hearing loss. There were 8 children with losses of 40-70dB in one of their ears but their better ear could detect 15-35 dB sounds. All the other PM children could hear from 10-25dB sounds on the better ear.

5. Please specify whether or not subjects with hearing thresholds exceeding 40 dB HL (PTA 1,2,4 kHz) were fitted with hearing aids and whether or not subjects with hearing thresholds exceeding 60 dB HL (PTA 1,2,4 kHz) were fitted with hearing aids. Test stimuli used do not exceed 70 dB SPL: please specify if subjects with hearing thresholds exceeding 40 and 60 dB (PTA 1,2,4 kHz) used hearing aids during auditory testing.

Unfortunately, in this rural Kenyan location, none of the children in the present study were fitted with hearing aids. Hearing aids aren’t normally fitted in children and that is why we were forced to exclude children with severe and profound hearing loss from the analysis.

6. Please specify age at which subjects were infected with PM.

The study subjects were between 5 and 15 years old and the study was carried out in 2006. The children had been hospitalized between 1994 and 2004. The majority of the children in the study area would have been exposed to PM when they are younger than 5 years old.
7. Discussion general: the discussion is far too long, please make it much shorter


The discussion highlights the main results of the study and discusses these in light of existing literature. We feel that a comprehensive discussion may be needed to provide a critical analysis of the results in a study of such great importance. However, we have cut down the number of words with over 120 words in the revised manuscript.

8. “Children exposed to PM had longer auditory P1 latencies than unexposed children. The P1 component has been thought to be an objective measure of cortical auditory function in children [28]. Longer P1 latencies in children with exposure to PM suggest slower or impaired development of their auditory functions. In general, there are age-related decreases in P1 latency with increasing age, which is shown in children studies [29-31]. These decreases can thus be viewed as the development of the auditory pathways [30].” Please study some of the more recent papers of e.g. Sharma et. al. These authors have produced many papers after 1997 which contain more relevant information.

We appreciate the reviewer’s comment and have included more updated reviews and papers on the subject in line with the suggestion.

9. P1 latency is considered to be a measure of auditory functioning. P1 latency decreases with the duration of auditory stimulation. Hence, in normal hearing subjects P1 latency decreases with age. In hearing impaired subjects P1 maturation only starts after adequate hearing rehabilitation. Therefore more specific information about the hearing status of the subjects, the age at which subjects were infected with PM and whether or not hearing impaired subjects word hearing aids (during test as well as in the period since PM) is essential for interpretation of the results. All this information is missing. Also note that part of the subjects included may not be able to hear the test stimuli (which do not exceed 70 dB SPL).

In the revised manuscript, we have included information about the children and that they had no hearing aids. In line with the reviewer’s suggestion, we have corrected some of the discussion on the P1 component. All the children included in the analysis were able to hear 70dB SPL sounds as the cut off was 60 dB SPL. The classification was mild impairment 26-40 dB, moderate impairment 41-60 dB, severe impairment 61-80 dB and profound impairment > 81 dB but had been reported otherwise in the previous manuscript. We have made corrections in the revised manuscript on page 3 paragraph 2.

10. P12 “In the present study, novel sounds (environmental noises) provided a deviation from the standard tones (1000Hz SPL) and target tones (2000Hz SPL)” Incorrect: should be 1000 Hz, XX dB SPL, please add dB and the actual sound
pressure level

The correction is appreciated and has been made in the first paragraph of page 12.

11. P13 “Limitation of the study” In the present study, children with profound to severe hearing loss were excluded from the ERP paradigms to minimize biases arising from sensory impairments. However, it is possible that subtle hearing loss and cortical blindness could have accounted for the differences in children with pneumococcal meningitis.”

In the revised manuscript on page 13 paragraph 2, we have added a sentence in the “limitations of the study” to address this issue. However, a peak-to-peak analysis of the auditory N2 component showed that the difference in the amplitude was independent of the P1 component which suggests poorer outcome in the children exposed to pneumococcal meningitis that is not entirely accounted for by subtle hearing loss.

12. Children with hearing loss up to 80 dB may be included in the study. This should not be referred to as “Subtle hearing loss” for the following reasons:

• Some of the subjects may not be able to hear the test stimuli
• Some of the subject may have had PM at young ages, causing hearing loss and auditory deprivation leading to unmatured P1 latencies.

It is the opinion of the reviewers that from the auditory potentials recordings it is not possible to conclude cognitive deficits are present. It is more likely that the average outcomes are influenced by hearing impaired subjects participating and reflect the results of auditory impairment during the test as well as lack of auditory stimulation in the past.

There was a major reporting error of the hearing thresholds which were only detected when the reviewer asked about the hearing loss of 80dB. I have since established from my co-author (EW) who did the screening of the children that the classification levels were; mild impairment 26-40 dB, moderate impairment 41-60 dB, severe impairment 61-80 dB and profound impairment > 81 dB. This correction has been made on the revised manuscript on page 3 paragraph 2.

13. References: please update ref 4-10 since there are much more recent papers on cognitive functions in bacterial meningitis

We have added updated articles on the long term effects of bacterial meningitis on cognition.