

Peer Review File

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Reviewer A

1. Thank you, this paragraph has been amended to reflect that there is extravasation across leaky/disrupted barriers.
2. I am unfamiliar with the Scandaniavian guidelines for children with severe traumatic head injury – the only reference that I can find is for incorporation of S100B in children with mild or moderate head trauma which is outside the scope of this review. I would be grateful if the Reviewer could provide a reference.
3. An extra sentence has been added following Line 167 to ensure clarity: *The greatest contribution to the peripheral signal most likely comes from those brain cell biomarkers derived from the brain interstitial fluid and cerebrospinal fluid.*
4. Thank you for drawing our attention to those articles. An extra sentence has been added: *Preliminary studies have shown that there is a correlation between salivary and serum S100B and the new references added as 18 and 19.*
5. The sentence now reads: *S100B is localised predominantly in astrocytic glial cells of the central nervous system and is specifically found in the cytoplasm and nucleus and thus will be present in brain interstitial fluid and cerebrospinal fluid.*
6. I am not aware of any publications that measured serum s100B in children with both severe TBI patients and other conditions outside the central nervous system that are known to cause an increase in serum S100B. I would be grateful if the Reviewer has any references.
7. Agreed, I have added the following sentence to the conclusion: *Serum S100B is the most studied biomarker to date and our study has shown that serum S100B shows promise as a diagnostic tool as serum S100B levels are significantly higher in children with severe TBI including children with inflicted and non-inflicted head injury. The last paragraph in the abstract now reads: Biomarkers are objective molecular signatures of injury that are released following traumatic brain injury and may represent a way of unifying the heterogeneity of traumatic brain injury into a single biosignature. Biomarkers hold promise to diagnose brain injury severity, guide intervention selection for clinical trials, or provide vital prognostic information so that early intervention and rehabilitation can be planned much earlier in the course of a child's recovery. Serum S100B is the most studied biomarker to date and this review has shown that serum S100B shows promise as a diagnostic tool with serum S100B levels significantly higher in children with severe TBI including children with inflicted and non-inflicted head injury.*

Reviewer B

1. The abstract and introduction have been revised as suggested.
2. The textbook references have been removed and replaced with recent review articles. It would be difficult to only include articles from the last 5 years as the literature pertaining to biomarkers in severe TBI is already limited. For example for S100B, out of 16 articles, only 3 would be included in this review and it would be extremely difficult to provide an overview that a clinician would find useful. However, if the reviewer and editors felt this was important, we could look at this again.
3. The title has been modified to incorporate both Reviewer B and Reviewer C's suggestions: "Serum Biomarkers in Severe Paediatric Traumatic Brain Injury – A Narrative Review"

Reviewer C

1. The title has been changed to reflect your comments and is now "Serum Biomarkers in Severe Paediatric Traumatic Brain Injury – A Narrative Review"
2. The introduction has been revised as per the suggestion of Reviewer B and is shorter and more succinct.
3. Line 139, further clarification has been added to the definition of biomarkers. This section now reads: A biomarker is 'a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention' (Robert Califf). Thus, biomarkers are objective molecular signatures of markers of injury that are released into the bloodstream following traumatic brain injury and may represent a way of unifying the heterogeneity of TBI into a single biosignature.
4. The section on ideal biomarkers has been amended to reflect Papa's work: This section now reads: Papa et al state that the ideal biomarker for traumatic brain injury would (1) have a high sensitivity and specificity for brain injury; (2) help stratify patients by severity of injury; (3) have a rapid appearance in accessible biological fluid; (4) provide information about injury mechanisms; (5) have well-defined biokinetic properties; (6) monitor progress of disease and response to treatment and (7) predict functional outcomes (17).
5. I have been through the manuscript and added the 95% CI for the AUC where they have been provided by the authors.
6. Could the reviewer be more specific in this comment? I believe that the two comments are consistent in that because S100B is found in peripheral locations, this limits its clinical usefulness. I have tried to present facts as an overview in the first section and then discuss the limitations to its usefulness in the following sections.
7. The literature that I have on GFAP record that it is specific to the astrocyte. Is the reviewer able to provide a reference.
8. Future Directions & Conclusion: these two paragraphs have been modified to incorporate the promise of S100B as a biomarker.
9. Tables: I have deliberately limited the information on the Tables so that these are not too difficult to read and absorb. I have provided references so that the reader may read further on the subject.