Reviewer’s report

Title: Brain biomarkers and pre-injury cognition are associated with long-term cognitive outcome in children with traumatic brain injury

Version: 0 Date: 05 Aug 2016

Reviewer: Paul van Donkelaar

Reviewer's report:

In this manuscript the authors have examined the relationship between serum biomarkers and long-term cognitive outcomes in youth TBI. In particular, they have assessed 6 serum biomarkers and determined whether changes in these biomarkers after the injury were associated with systematic variations in cognitive function as assessed with clinical questionnaires probing parents' perceptions of their child's abilities. The results showed that increases in neuron specific enolase (NSE) and decreases soluble neuron cell adhesion molecule (sNCAM) within days post-injury significantly predict poorer parent-rated performance on scales of inattention, hyperactivity/impulsivity, executive function, working memory, and initiate scores 3 years after the injury. Based on these observations, the authors concluded that BSE and sNCAM are reliable predictors of long-term cognitive outcomes in youth TBI.

This is a very well-written manuscript the results of which provide new insight into the capacity of blood biomarkers to predict long-term outcomes in TBI. I have several comments which I think will significantly strengthen the manuscript prior to publication:

1. The authors have limited their assessments to participants with TBI and associated injuries. However, they do not include a control group with these injuries but without TBI. This is an important consideration because the blood biomarker alterations could be due to non-specific effects of injuries rather than TBI per se. Ideally, a control group as outlined should be collected. At the very least a detailed discussion the potential non-specific effects of injury on the blood biomarkers that were collected is warranted.

2. It is unclear how many of the participants only had one blood draw and when that draw was made relative to the injury. Given the manner in which different biomarkers respond to injury over different time courses, this information is very relevant to determining their predictive capacity.

3. It would be helpful to see data from individual participants from Table 2 plotted over time. This is especially relevant determining the nadir of sNCAM. Additional references supporting the temporal dynamics of sNCAM is also warranted.
4. The age range of the participants is rather large. Given the neurodevelopment process, it is likely that there were some age-related differences across the measures obtained. Some assessment of these potential developmental responses to TBI is warranted.

5. Given that NSE is increased immediately following a bout of exercise, some assessment of activity levels immediately preceding injury should be included.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal