Reviewer’s report

Title: Hypopituitarism after subarachnoid haemorrhage (SAH), do we know enough? a systematic review

Version: 1 Date: 22 April 2014

Reviewer: Randall J Urban

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Reviewers: Randall J. Urban, MD, William J. Durham, PhD, and E. Lichar Dillon, PhD.

The authors performed a systematic review of literature published between 1995 and 2012 concerning pituitary dysfunction following subarachnoid hemorrhage (SAH). A total of 12 studies were included in the final review based on the search criteria selected. The stated aim was to clarify the occurrence, pattern and severity of endocrine abnormalities and to identify risk factors for hypopituitarism after SAH. Based on the review, the authors concluded that neuroendocrine dysfunction may be a determinant of poor functional outcome following SAH but that more prospective studies are needed to assess incidence, clinical course, and effect on mood, behavior, and quality of life.

The aim of the review is highly clinically relevant, however, there are a number of systematic issues that need to be addressed that would improve the quality of this review.

Major Compulsory Revisions

Overall, the review is fairly fragmented and superficial (possibly due to the diversity of the findings in the manuscripts included in the review) and while identifying many areas of agreement vs. divergence in the literature (i.e. methodologies, statistical analyses, diagnostic criteria used, patient characteristics, etc) there could be more time spent detailing how these differences impacted the conclusions of the individual reports as well as that of the current review.

1. The authors identified 12 studies describing “pituitary function” in the long term after SAH. However, the search terms reportedly used may have selectively included reports where negative correlations were found. i.e. how would a focus on more neutral search terms such as pituitary function instead of hypopituitarism, and thyroid function instead of hypothyroidism affect the MEDLINE search and final inclusion of manuscripts in this review?

2. The authors mention differences in patient selection and selection bias between the studies included in the review. Please elaborate on which criteria were used to identify patients and how pituitary dysfunction was diagnosed in the studies.
3. In the 1st paragraph of Results, lines 141-142. The authors state that “43 articles did not report relevant endocrine or functional outcome.” Notably, in the Methods section under “Selection criteria” (lines 121-8), “functional” outcomes are not mentioned. The authors should clarify whether functional outcomes were part of the selection criteria or, alternatively, whether all of the 43 articles were excluded due to lack of relevant endocrine outcomes.

4. Discussion, first paragraph. The authors state that “studies we evaluated in this review all showed evidence” for pituitary dysfunction (line 191), yet, later in the paragraph, that the “prevalence of hypopituitarism varied from 0-55%...”. The idea that the prevalence of pituitary dysfunction in one or more of the 12 studies was 0% seems incongruous with the statement that all studies showed evidence of pituitary dysfunction. The authors need to clarify whether there were in fact some studies that failed to show evidence of pituitary dysfunction or how “all” and “0%” can both be correct. Were there statistically significant differences in pituitary function between SAH patients and controls in one or more studies in which that pituitary function was nevertheless not low enough to be classified as hypopituitarism in the SAH patients?

5. The authors conclude that neuroendocrine function may be an important and modifiable determinant of poor functional outcome after SAH. However, the authors mention that none of the studies included in the analysis addressed treatment options or modifications and on line 250 the authors mention that “there were no studies reporting functional long-term outcome...”. Since the authors specify that the review is aimed at assessing incidence, clinical manifestations, and risk factors the conclusions should refer back to the findings with respect to the stated aims of the review.

Minor Essential Revisions

1. 5th paragraph, lines 98-103. There are many statements made in this section that need to be supported by references. If the references (#20-23) cited at the end of the paragraph also refer to these statements, they need to be listed at the end of each sentence or claim, as appropriate.

2. Results section, under “Frequency and type of hypopituitarism...”, line 161. It appears that a question mark was inadvertently placed after “510” and should be removed (or the number finalized, if it indicated uncertainty).

3. Line 191: Not all the studies in the review showed evidence for neuroendocrine dysfunction. This sentence should read something like “11 out of 12 studies...”

4. Discussion, line 247. The authors should provide a reference for the statement that the relevance of pituitary dysfunction after SAH is unclear.

5. Discussion, last 2 paragraphs. In the penultimate paragraph, the authors state that there are no studies designed to answer the question of whether SAH is a risk factor for future hypopituitarism. However, in the final paragraph, the authors
conclude that “SAH seems to be associated with increased risk of endocrine dysfunction”. The authors should clarify their message here. Are they making a distinction between pituitary and non-pituitary endocrine dysfunction following SAH?

Discretionary Revisions
1. 2nd paragraph, line 70. Missing words in line reading “…, the inability of the pituitary gland to sufficient hormones…” Suggest “gland to produce sufficient hormones to meet the needs…”

2. Paragraph starting on line 75 is unnecessary and distracting from the message of the surrounding paragraphs. Suggest moving this paragraph to another section of the manuscript or omitting altogether.

3. 5th paragraph, line 97. “Nevertheless” seems more appropriate than “As such”.

4. Results, line 166. Suggest placing “an average of” between “for” and “14”.

5. Results, lines 183-184. “40 patients” is used redundantly in the same sentence; suggest removing one instance.

6. Results, lines 197-199. Based on the summary of the studies evaluated in Table 2, it doesn’t appear that time per se is responsible for the differences between studies (e.g. even if one looks at the studies reporting results from 12 or 12-24 months post-SAH, there is considerable variation).

7. Many paragraphs appear fragmented and some are as short as a single sentence (i.e. line 219). Some of these can be easily combined into the existing paragraphs to facilitate readability of the manuscript.

8. Discussion, line 244. It seems that selecting patients based on symptoms could lead also lead to overdiagnosis of hypopituitarism in some cases.

9. Table 1: Please clarify “Lost to FU nr”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.