Author's response to reviews

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

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Author's response to reviews: see over
Response to the reviewers
We thank all reviewers for their valuable comments. We discuss their comments below. Page numbers refer to the revised version of the manuscript.

Reviewer 1: ZULEYHA KARACA

Comment 1
SAH is usually associated with single hormone deficiencies such as GH rather than multiple deficiencies. This should be clearly emphasized in the discussion and conclusion parts.

Response:
We agree with you that SAH is more often associated with single hormone deficiencies rather than multiple, however in a small but considerable proportion of patients multiple axes are affected. We have added the following sentences to the review.

Changes to the manuscript:
Page 7 line 212-213: added sentence: “Single hormone deficiencies, mainly GHD, were more frequently found than multiple hormone deficiencies”
Page 8 line 238-240: Intriguingly, single deficiencies were more often described than multiple hormonal deficiencies. This may imply that specific parts or systems of the anterior lobe of the pituitary gland are more vulnerable to damage than others.

Comment 2
There are many spelling and linguistic errors. The manuscript needs to be checked for linguistic errors carefully.

Response:
We thank you for this recommendation. We have thoroughly checked the manuscript for spelling and linguistic errors and made changes where appropriate.

Changes to the manuscript:
Page 3 Line 70: removed: has been related to and added: associations have been made
Page 3 line 73: added the word “produce” to the sentence: gland to produce sufficient hormones to meet the needs.
We removed paragraph starting at line 75 as it was distracting of the main message. We used some part of it in the discussion part of the manuscript: page 7 line 215-226
Reviewer 2 GIANLUCA AIMARETTIE

Comment 1

I suggest to focus the discussion section more on the disease follow SAH, I mean hypopituitarism, more than on GHD. GHD could be considered as a signs of hypopituitarism able to evidence a more complex disease frequently involving all anterior pituitary dysfunction.

Response:

We absolutely agree with the reviewer that endocrine dysfunction after SAH is more than only GHD. It involves other endocrine axes as well, though in the majority of cases it seems to involve dysfunction of the anterior lobe more than the posterior lobe, nevertheless the posterior lobe can also be affected. We have added a paragraph concerning this subject and we have re-written the introduction and discussion to elaborate more on this subject.

Changes to the manuscript:

Page 7 line 215-228 has been re-written and replaced by: Several mechanisms may lead to altered pituitary function in patients with SAH. Endocrine dysfunction may be provoked by compression of the hypothalamic-pituitary complex by the aneurysm itself, post-haemorrhagic local tissue pressure changes, toxic effects of extravasated blood, ischemia caused by vasospasm, increased intracranial pressure, hydrocephalus, or local destruction during craniotomy. The pituitary gland is divided into an anterior and posterior lobe. The anterior lobe is responsible for producing several peptide hormones: ACTH, TSH, prolactin, GH and gonadotropin hormones: LH and FSH. The posterior
pituitary is a storage organ for the ADH and oxytocin.[20] The pituitary gland is supplied with blood from the branches of the internal carotid artery, which form a capillary plexus in the region of the median eminence of the hypothalamus. Blood from this area reaches the anterior pituitary by means of long and short portal veins through the pituitary stalk. The middle and inferior hypophyseal arteries supply the pituitary stalk and neurohypophysis with arterial blood.[20] This difference in blood supply might play a role in the pathophysiology of endocrine dysfunction after SAH, because it is the anterior pituitary hormones that are more often affected after SAH.

Page 8 line 238-242: Intriguingly, single deficiencies were more often described than multiple hormonal deficiencies. This may imply that specific parts or systems of the anterior lobe of the pituitary gland are more vulnerable to damage than others. On the other hand, the single anterior pituitary axe deficiencies may be a marker of multiple deficiencies, which are not detected due to inappropriate testing.

Comment 2
I wonder if some details on posterior pituitary dysfunction could be added.

Response:
We have added more background information about posterior pituitary dysfunction to the discussion in addition to your first comment.

Changes to the manuscript:
Page 7 line 228-238 added sentences: Nevertheless, posterior pituitary can also be affected. Hyponatremia is a common symptom in the early phase of SAH.[51] The exact mechanism of this complication after SAH is still poorly understood. There are different theories about the cause of this symptom. Different study groups have suggested syndrome of inappropriate antidiuretic hormone secretion as the main cause of hyponatremia after SAH.[52, 53] Yet others have suggested cerebral salt wasting syndrome due to the rise of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) together with volume depletion through ADH hypo-secretion.[54-58] Furthermore, due to the presence of ACTH deficiency in the early phase after SAH[42, 59], ACTH deficiency has also been mentioned as one of the possible mechanisms for developing hyponatremia. Clinical evidence for this theory is lacking and needs further evaluation[53].

Reviewer 3 RANDALL J URBAN, ET AL.
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.

Comment 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?

Response:

We did a new search of pubmed using neutral terms as you suggested. We used the following search:

("subarachnoid hemorrhage"[ All Fields] AND "pituitary"[ All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "hypopituitarism"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "growth hormone"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "testosterone"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "cortisol"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "diabetes insipidus"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "thyroid function"[All Fields]) OR ("subarachnoid hemorrhage"[ All Fields] AND "diabetes insipidus"[All Fields]) from 1995 up to 2012.

We found 168 articles, after screening these articles using our pre-determined inclusion criteria, we did not find any additional articles which reported original data concerning pituitary function in the chronic phase after SAH.

After that we did a new search, using your suggestion and included articles up to now. We now screened 194 articles and found 3 more articles reporting original data. We revised the manuscript according to the new search terminology suggested by you and the new findings.

Changes to the manuscript:

Line 42: added: “growth hormone, gonadotropin, testosterone, cortisol, thyroid function and diabetes insipidus” to the abstract and removed: “deficiency, hypogonadism, hypercortisolism, hypothyroidism”.

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Line 95-97 added: “pituitary function, hypopituitarism, growth hormone, pituitary function, thyroid function, growth hormone, cortisol and testosterone function and or diabetes insipidus”.

Page 4 Line 124: added: Initially 194 citations (abstracts) were found. Of these citations, 62 articles did not report relevant endocrine outcome. Eighty-eight studies concerned other diseases than aneurysmal SAH. Eighteen case reports were also excluded. Twenty-six full-text articles were collected of which 5 articles reported only early phase endocrine dysfunction [23-27], 3 were review articles [28-30], 1 article reported combined data of SAH with traumatic brain injury [31] and 1 large study was excluded because it concerned an internet based data collection study [32]. Finally sixteen studies fulfilled the inclusion criteria and were eligible for the current review (figure 1).

Page 4 Line 133-134: added: Seven studies were cross-sectional or retrospective cohort studies [18, 33-38]. Nine studies were conducted prospectively [39-47].

Page 6 Line 192-193: added: Kronvall et al. reported that younger age was significantly associated with pituitary dysfunction at follow up

Table 1, table 2 and figure one were adjusted according to the new findings.

Comment 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.

Response:

Two studies with the most appropriate design were already discussed in more detail on page 7 line 243-249. To elaborate on this topic in the other studies, we have added the following section to the review.

Changes to the manuscript:

Page 5 and 6, line 137-164: Dimopoulou et al. retrospectively analyzed 30 patients between one and two years after SAH but did not use a stimulation test for the evaluation of growth hormone function. [18] Aimaretti et al. conducted a prospective follow-up study of 40 patients after SAH derived from multiple Italian centres. The patients were all conscious and measured 3 months after discharge from the ICU GHRH+ arginine test was used to measure growth hormone function [38]. Aimaretti et al. prospectively studied 32 patients in Italian hospitals, and performed basal hormonal tests and GHRH+arginine test as dynamic test to establish GHD between 3 and 12 months after SAH. [33] Brandt et al. selected 10 patients with fatigue after SAH and measured corticotrophin, growth hormone and thyrotrrophic function using insulin tolerance test (ITT) and TSH-Thyroid releasing hormone stimulation tests 12 month after SAH. In 30% of the patients ITT was not performed. [34] Kreitschman-Andermahr et al. retrospectively studied 40 SAH patients from a cohort of 274 patients.
after excluding patients with liver disease, coronary heart disease, convulsions, DM, depression, severe confusional state or vegetative state after discharge. ITT and THRH-LHRH were used as dynamic tests for assessment of ACTH, TSH and GH function 12 to 72 months after SAH.[36] Kreitschman-Andermahr et al. retrospectively measured basal hormones in 45 patients 3 to 24 months after SAH. Only 14 patients had dynamic tests.[37] Jovanovic et al. retrospectively evaluated endocrine function in 93 patients, between one and ten years after SAH, however stimulation tests were not used[35]. Tanriverdi et al. prospectively analysed 22 patients one year after SAH using basal and dynamic tests for ACTH and GHD.[41] Karaca et al. did a follow-up study, three years after SAH of 20 patients investigated by Tanriverdi et al. in the abovementioned study using basal hormonal tests and glucagon stimulation test[47]. They found 4 cases of GHD three years after SAH of whom three did not have GHD one year after SAH. Dutta et al. evaluated endocrine function in 60 SAH patients with anterior communicating artery (A-com) and middle cerebral artery (MCA) aneurysms using only basal hormonal tests. Part of the study was retrospective, analyzing patients one year after SAH and partly prospectively analysing patients 6 months after SAH.[48]. Kronvall et al. prospectively analysed 45 patients in the acute phase and 3 to 6 months after SAH, using basal hormonal test and GHRH-arg test for GHD. They did not use a dynamic test to establish ACTH deficiency [46], Khursheed et al. prospectively analyzed 73 patients nine months after SAH for TSH and gonadotropin deficiency and not the other anterior pituitary hormones.[45] Blijdorp et al. prospectively analysed 84 patients and reported preliminary data of 43 patients using basal hormonal tests, synacten test when ACTH deficiency was suspected and a ghrelin test in the early phase after SAH and confirmatory GHRH-arg test after six months.[44]

Comment 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.

Response:
You are correct. Our search criteria did not include functional outcome. We looked for articles concerning pituitary function, in these articles we searched for further results concerning the functional outcome. As functional outcome was not our primary outcome, we have corrected this in the results section.

Changes to the manuscript:
Page 4Line 123: removed: or functional outcome.
Comment 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?

Response:

In one of the articles which was assessed in this review, the long-term frequency of pituitary deficiency was 0%. However, they found Early post-SAH hormone anterior pituitary function in 58% of the SAH patients. But they were not able to find any sign of hypopituitarism in their confirmatory testing at 12-24 months after SAH. Therefore they concluded that no chronic hypopituitarism was observed [8]. Although they did not find any sign of persistence of pituitary deficiency, they did find an alteration of the endocrine function early after SAH. We agree that this is not reported clearly in our review.

Changes to the manuscript:

Page 7 Line 207-209: added: From the 16 studies we evaluated in this review, 15 showed some evidence for neuroendocrine dysfunction on one or more pituitary axes in the long term after SAH. In one study neuroendocrine dysfunction was only present in part of the patients in the early phase and not in the long-term after SAH.

Comment 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.

Response:

We agree with the reviewers on this point. This line does not refer back to our findings. It is a speculation, which was meant to underline the possible importance of acknowledging endocrine
dysfunction after SAH to be a possible modifiable determinant of long lasting physical complaints after SAH. We have removed the sentence mentioned above.

Changes to the manuscript:
Page 9 Line 294: removed: However, neuroendocrine dysfunction may turn out to be an important modifiable determinant of poor functional outcome.

Minor Essential Revisions

Comment 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.

Response:
We have re-edited the reference list in this section and listed the reference to each sentence.

Changes to the manuscript:
Page 3 line 74-82: Adrenocorticotropic (ACTH) and thyroid stimulating hormone (TSH) deficiency may cause fatigue, weakness, headache, altered mental activity, and impaired memory[20, 21]. Growth-hormone deficiency (GHD) may cause lack of vigour, fatigue, decreased exercise tolerance and decreased social functioning[20, 21]. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency in women lead to oligomenorrhea, dyspareunia, infertility and loss of libido. Testosterone deficiency in men can present with impaired sexual functioning, mood impairment, and loss of libido[20, 21]. Antidiuretic hormone deficiency (ADH) leads to polyuria and polydipsia.[20-22].

Comment 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).

Response:
We have corrected this error.

Changes to the manuscript:
Page 6 Line176: question mark was removed.
Comment 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…”

Response:
The reviewer is right. We adjusted this sentence in reply to your earlier suggestion (point 4 of major compulsory revisions).

Changes to the manuscript:
Page 7 line 207-208 added: From the 16 studies we evaluated in this review, 15 showed some evidence for neuroendocrine dysfunction on one or more pituitary axes in the long term after SAH.

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

Response:
We have added a reference to a paper written by Noble et al. In this meta-analysis about the variables that could explain the poor health related quality of life, they state that a more thorough investigation of this possible determinant is needed

Changes to the manuscript:
Line 290 reference 67.

Comment 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?

Response:
Almost all studies we have discussed showed some evidence of hypopituitarism. However, none of them had the proper case-control design to irrefutably show an association between SAH and hypopituitarism. That is why we used the word “seems” in the last paragraph.
Changes to the manuscript:
We added the words “case-control” to the sentence in the penultimate paragraph

Discretionary Revisions

Comment 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…”

Response: The reviewer is right. We corrected this error.

Changes to the manuscript:

Page 3 line 71-72: gland to produce sufficient hormones to meet the needs

Comment 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.

Response: we agree with you that this paragraph is distracting. We have re-written and revised this paragraph and moved it partly to the discussion, we have used this paragraph to elaborate on the possible mechanism of pituitary deficiency after SAH.

Changes to the manuscript:

Page 3 paragraph starting at line 75, removed the paragraph as suggested by the reviewer.
Page 7 line 283-327: added paragraph Several mechanisms may lead to altered pituitary function in patients with SAH. Endocrine dysfunction may be provoked by compression of the hypothalamic-pituitary complex by the aneurysm itself, post-haemorrhagic local tissue pressure changes, toxic effects of extravasated blood, ischemia caused by vasospasm, increased intracranial pressure, hydrocephalus, or local destruction during craniotomy. The pituitary gland is divided into an anterior and posterior lobe. The anterior lobe is responsible for producing several peptide hormones: ACTH, TSH, prolactin, GH and gonadotropin hormones: LH and FSH. The posterior pituitary is a storage organ for the ADH and oxytocin.[20] The pituitary gland is supplied with blood from the branches of the internal carotid artery, which form a capillary plexus in the region of the median eminence of the hypothalamus. Blood from this area reaches the anterior pituitary by means of long and short portal veins through the pituitary stalk. The middle and inferior
hypophyseal arteries supply the pituitary stalk and neurohypophysis with arterial blood. [20] This
difference in blood supply might play a role in the pathophysiology of endocrine dysfunction after
SAH, because it is the anterior pituitary hormones that are more often affected after SAH.
Nevertheless, posterior pituitary can also be affected. Hyponatremia is a common symptom in the
early phase of SAH. [51] The exact mechanism of this complication after SAH is still poorly
understood. There are different theories about the cause of this symptom. Different study groups
have suggested syndrome of inappropriate antidiuretic hormone secretion as the main cause of
hyponatremia after SAH. [52, 53] Yet others have suggested cerebral salt wasting syndrome due to
the rise of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) together with
volume depletion through ADH hypo-secretion. [54-58] Furthermore, due to the presence of ACTH
deficiency in the early phase after SAH [42, 59], ACTH deficiency has also been mentioned as one
of the possible mechanisms for developing hyponatremia. Clinical evidence for this theory is
lacking and needs further evaluation [53]. Intriguingly, single deficiencies were more often
described than multiple hormonal deficiencies. This may imply that specific parts or systems of the
anterior lobe of the pituitary gland are more vulnerable to damage than others. On the other hand,
the single anterior pituitary axis deficiencies may be a marker of multiple deficiencies, which are
not detected due to inappropriate testing.

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

Response: we have used your suggestion.

Changes to the manuscript:
Page 3 line 86: added: nevertheless, removed: of as such.

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

Response: we have used your suggestion.

Changes to the manuscript:
Page 6 line 181: “an average of” is added to the sentence.

Comment 5
Results, lines 183-184. “40 patients” is used redundantly in the same sentence; suggest
removing one instance.
Response: we have used your suggestion.

Changes to the manuscript:

Page 7, line 200: “in 40 patients” is removed from the sentence.

Comment 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).

Response: we agree that time is not the only variable responsible for the found differences in the studies. As all the studies used different stimulation tests and also different cut off value, it is very difficult to compare the articles. As you already stated: ‘due to the diversity of the findings in the manuscripts included in the review’ it is very difficult to compare the studies. We do think that different evaluation times leads to a change in the frequency of patients with pituitary dysfunction as for example found by Klose et al.

Changes to the manuscript:
We did not make any changes to the manuscript.

Comment 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.

Response: We have added the fragmented paragraphs to existing paragraph to make the reading of this article easier.

Changes to the manuscript:
Paragraph line 69 added to next paragraph starting from line 75 and partially rewritten and added together with paragraph starting from line 96 in the last manuscript.
Paragraph line 196 added to the next paragraph: in the new manuscript starting at line 243..
Paragraph line 218 added to the next paragraph: in the new manuscript starting at line 264
Paragraph line 235 has been rewritten: in the new manuscript starting at line 280
Paragraph line 249 added to next paragraph: in the new manuscript starting at line 291
Comment 8
Discussion, line 244. It seems that selecting patients based on symptoms could lead also lead to overdiagnosis of hypopituitarism in some cases.
Response: You are correct, if patients were only eligible when there are signs and symptoms of hypopituitarism in a study a selection bias will be introduced.

Changes to the manuscript:
Page 9 line 280-289: we have re-written the paragraph:
In general, patients with hypopituitarism may have many different symptoms, including for instance fatigue, impairment of concentration, infertility, weight gain and hair loss. For clinicians, it might be efficient to use the clinical symptoms of hypopituitarism to select patients for further endocrine evaluation. However the symptoms are non-specific and do not indicate the presence or type of endocrine dysfunction accurately. In a study in which patients were selected for endocrine evaluation based on clinical symptoms of hypopituitarism[37] the reported prevalence of pituitary dysfunction was approximately 30%. This is in accordance with other studies, in which patients were not selected based on symptoms. This suggests that selection based on clinical symptoms is not efficient. On the other hand there is insufficient evidence to support routine assessment of pituitary function in all SAH patients, because the clinical relevance of pituitary dysfunction after SAH is largely unclear[59].

Comment 9
Table 1: Please clarify “Lost to FU nr”
Response: We have added the following text to table 1

Changes to the manuscript: Number of patients lost in follow up of studies with more than one measurement overtime.


