Author's response to reviews

Title: Prevalence of hypopituitarism after intracranial operations not directly associated to the hypophyseal gland

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Author's response to reviews: see over
Dear Dr. Liatis,

We are very appreciative of the possibility to submit a revision of our manuscript. We would like to thank the editors and reviewers for their helpful comments concerning our manuscript. We have extensively revised our manuscript, addressed the comments, and have performed the necessary editing. We are sure that this publication considerably benefits by the reviewing process. Enclosed you will find the revised version of the manuscript as well as our responses to the reviewers’ suggestions. New changes to the manuscript are marked in yellow. All authors consented to the changes introduced. If there are further comments and suggestions, we are happy to address them.

Below are our responses to the REVIEWER COMMENTS and the related revisions that were made. All comments were carefully worked out and changes have been applied and/or discussed below. Reviewer comments have been repeated in 10pt Arial font in boxes; our own comments follow in 12pt Times. Revisions in the manuscript were marked in yellow.

REVIEWER #1 Charles Wilkinson

During the past decade, research findings and general awareness of a high prevalence of hypopituitarism after traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) have increased considerably. Recent studies have also found pituitary insufficiency in significant numbers of patients after intracranial operations and radiation treatment of non-pituitary tumors. This manuscript presents findings of a prevalence of hypopituitarism following non-pituitary intracranial procedures of 64.7%. The manuscript will provide an important contribution to increasing the knowledge base and awareness of the marked clinical significance of the vulnerability of pituitary function to neurosurgical procedures in addition to TBI and SAH.

Discretionary (but highly recommended) Revisions

One of the difficulties in evaluating and comparing the results of studies of posttraumatic hypopituitarism (PTHP) is the considerable variation in screening criteria used (Kokshoorn NE, et al. Eur J Endocrinol 162:11-18, 2010) and the frequent absence of sufficient detail about the criteria. In light of that problem, my suggestions for revision of this manuscript consist almost entirely of requests for more methodological detail regarding endocrine assessments.

1 Please specify the fT4 reference range and the criteria used for identifying "normal or low normal" TSH and "low" LH and FSH.

We thank the referee for his time to evaluate our manuscript. Please excuse, our previous formulation was disadvantageous. We adapted the manuscript and describe the fT4 reference range and the usage of TSH, LH and FSH now in more detail. We used the reference ranges for fT4 and TSH published 2010.

“Thyrotrophic deficiency was manifestly when fT4 were below the lower reference range [Völzke H, et al. Horm Metab Res 42(11):809-14, 2010] in combination with an inappropriately normal or low normal TSH. That means TSH is within the reference range and not increased as expected for primary hypothyroidism. Hypogonadism in men was defined as low testosterone (< 10 nmol/l) in combination with inadequate low gonadotropins (LH, FSH) [Partsch CJ, et al. J Clin Endocrinol Metab 60:1196-203, 1985].”
A substantial number of investigators feel that low (or high) dose ACTH tests fail to achieve acceptable levels of sensitivity and specificity to be adequate screening tests for secondary adrenal insufficiency (Suliman AM, et al. Clin Endocrinol (Oxf) 56:533-539, 2002; Dorin RI, et al. Ann Intern Med 139:194-204, 2003). Also, studies utilizing ROC analysis have found that basal morning serum or salivary cortisol provided a highly specific diagnosis "similar to the ITT result" (Deutschbein T, et al. Horm Metab Res 41:834-839, 2009; Dullaart RP, et al. Clin Endocrinol (Oxf) 50:465-471, 1999). These findings perhaps represent a minority opinion, but they deserve acknowledgment in the context of evaluation of PTHP. Please provide a reference for the statement that "the low dose ACTH test used here has been noted to correlate highly with the ITT." Also, please provide summary data indicating how many patients in the study were assessed to have secondary adrenal insufficiency as indicated by basal cortisol levels, by ITT results, or both.

Thank you very much for your advice. We added references that underline the current knowledge of the low dose ACTH test.


Furthermore, we have revised the paragraph Evaluation of Pituitary Function: “Twenty one patients underwent ITT, thirty patients underwent low dose ACTH test, and all patients underwent GHRH and arginine test.”

We also added data in result section: “Adrenocorticotrophic deficiency, in varying degrees, was observed in 51.0% of patients (partial 41.2%, complete 9.8%). No patient in the present study had baseline cortisol < 100 nmol/l, therefore, we could not identify any patient to have secondary adrenal insufficiency as indicated by the basal cortisol level. The diagnosis of adrenocorticotrophic deficiency in all patients is provided by dynamic testing.”

The reviewer raised a very interesting issue. The interval after surgery until testing ranges from 5 to 168 months. We analysed our data with respect toward a lower frequency of observed adrenal insufficiency in patients tested at longer intervals after surgery. However, we did not find any evidence of such a tendency. We observed no significant difference between groups after 24 (p=0.4654) and 48 months (p=0.1441) (Fisher test). For this particular question the number of patients investigated in the present study might be too low to detect frequency changes in relation to time.

Were low IGF-I levels predictive of ITT results? How many of the patients characterized as growth hormone deficient by the ITT or combined GHRH/arginine test were found to have low basal IGF-I levels (more than 2 SD below age-adjusted mean values)?

We thank the reviewer for his comment. There were differences between subjects with low IGF-I measurement with respect to the results of dynamic testing.
Three patients had IGF-I levels more than 2 SD below the norm for their age- and sex-group and provocative testing revealed severe GHD. These patients had additional pituitary insufficiencies, what support the diagnosis of GHD. Moreover, we observed six patients with low IGF-I but normal results of dynamic testing. Low IGF-I levels are indicative of pituitary deficiency, but they also may be caused by other diseases. However, this was not the aim of our study. Therefore, we do not add this data in the manuscript.

REVIEWER #2 Veit Rohde

The authors performed a prospective study investigating pituitary function in 51 patients after surgery for a variety of non-sellar pathologies; the hormone testing was performed 5 to 168 months after the operation. Some patients additionally underwent radiotherapy and chemotherapy. The authors detected hypopituitarism in two-thirds of the patients and concluded that hypopituitarism occurs frequently after brain surgery.

Two similar studies with the same results already had been published (Schneider 2006 [referenced by the authors] and De Marinis 2006 [not referenced]). Despite the prospective design, the authors failed to eliminate the substantial flaws of the proceeding studies. These flaws are 1- lacking preoperative data, 2- no defined time point of testing, 3- inclusion of patient who have undergone radiotherapy which might have the sequel of hypopituitarism. As a consequence the conclusion that brain surgery is the culprit of hypopituitarism is not sufficiently substantiated.

Furthermore, there exist one prospective, again not referenced trial in 54 patients in which preoperative testing and testing 1 and 7 days after surgery was performed (Wachter 2011). This study design eliminated many of the flaws of the previous two and of this study and indicated that almost 50% of hypopituitarism already is present before surgery.

We thank the reviewer for the careful evaluation of our manuscript and his advices.

We fully agree with the reviewer’s comment regarding the limitations of our study. It is correct that we did not use defined time point of testing and that we included patient who have undergone radiotherapy and chemotherapy. However, in our opinion this reflects the conditions of clinical practice. Furthermore, currently there are no recommendations for optimal time point of testing. The requirement of establishing optimal time points for evaluation the pituitary function was added to the conclusion paragraph.

“We want to appeal to perform other prospective studies with a larger number of patients and with implementation of pre-operative testing. From our point of view, guidelines for example with recommendations for optimal time point of post-operative testing are required.”

The reviewer mentioned that previous studies confirmed that patients with intracranial operations not directly associated with the pituitary gland are at higher risk for hypopituitarism. Now we added these additional references in the revised manuscript. We would respectfully point out, that Schneider 2006, De Marinis 2006 and Wachter 2011 had evaluated only a few patients, all together 159 subjects. We are not convinced that these are enough scientific data to increase the knowledge of the marked clinical significance of the vulnerability of pituitary function to neurosurgical procedures. We have revised the introduction.

“Schneider et al. assessed endocrine abnormalities in 68 patients who underwent surgery for non-pituitary intracranial tumors while also receiving chemotherapy or radiation and found that over 40% of all patients had hormone irregularities [Schneider 2006]. However, studies investigating the frequency of pituitary insufficiency after intracranial operations for non-pituitary tumors are limited [De Marinis 2006, Wachter 2011] which highlight the need of more data. Therefore, we sought to prospectively determine the frequency of hypopituitarism and hypopituitarism-related factors in post-operative patients using basal parameters and advanced pituitary function tests.”
In addition we expanded the discussion.
“It has been suggested that screening for hypopituitarism (performed within 21 days after brain injury as well as 12 weeks and 12-month post-operative) is necessary [Aimaretti 2005, Ghigo 2005]. We performed testing between 5 and 168 months (mean 47.2) after the procedure to evaluate possible longstanding hormonal deficiencies closer to the clinical practice. Wachter et al. postulated that pituitary insufficiencies are already present before surgery but they performed the evaluation only 1 to 7 days after surgery which might have the potential to underestimate the frequency of hypopituitarism.”

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Hopefuly, these comments serve to convince the reviewers to consider the data and results of this study for publication in *BMC Endocrine Disorders*.

All references are from the manuscript.

With kind regards, Steffen Fleck (for the authors)