Reviewer’s report

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

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Reviewer: Charles Wilkinson

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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.

2. 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.

3. In general, adrenal insufficiency is one of the most frequent endocrine disorders observed acutely after brain injury but one of the least frequent found in chronic PTHP, and there are several reports of resolution of adrenal insufficiency with time after trauma (e.g., Tanriverdi et al. Clin Endocrinol (Oxf) 68:573-579, 2008; Hannon et al., J Clin Endocrinol Metab, published ahead of print May 20, 2013 as doi:10.1210/jc.2013-1555). Was there any indication of a tendency toward a lower frequency of observed adrenal insufficiency in patients tested at longer intervals after surgery?

4. 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)?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.