Hypopituitarism : clinical assessment in different conditions

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Chapter 8

General discussion and summary

Contents

I. Introduction

Many tests are available for the assessment of pituitary function. The thyroid, gonadotropic and prolactine axes can be appropriately assessed by the combination of clinical symptoms and unstimulated serum hormone levels. However, stimulation tests are mandatory for appropriate evaluation for the assessment of the HPA and GH-IGF-I axes (1).
Different stimulation tests are available, for which different cut-off values have been reported. When using a stimulation test, it is of great importance to take other confounding factors into account such as age, gender, BMI and medication. GH secretion decreases resulting in lower serum levels with increasing age and BMI (2–4). Medication can alter hormone levels and therefore influence test outcome. The pituitary gland does not necessarily be stable, but can change over time, e.g. after traumatic brain injury (TBI) or pituitary surgery (5;6). Consequently, pituitary stimulation tests performed immediately after surgery may give altered results. In this thesis several studies are reported aiming to provide better insight into the complexity of different endocrine tests used for the evaluation of possible pituitary insufficiency and in the treatment of patients with pituitary insufficiency.

II. Evaluation of pituitary function in patients after Traumatic Brain Injury (TBI)

After TBI patients experience persistent, invalidating complaints that resemble those observed in patients with hypopituitarism, such as impaired cognition, depression, fatigue and impaired quality of life (QoL) (7–9). Consequently, pituitary insufficiency following TBI may contribute to the problems reported by these patients. This condition is important to identify since it can be treated by hormone replacement therapy resulting in improved QoL (10).

In the past decade a high prevalence of pituitary insufficiency following TBI has been reported (11–24). However, there is great variation in the reported prevalence rates. Several factors influence the prevalence of hypopituitarism after TBI: the time interval between TBI and endocrine assessment, the type and severity of the trauma and also the methods (*i.e.* endocrine tests, assays and criteria) used for the diagnosis of hypopituitarism. Some reviews have addressed TBI-related hypopituitarism and concluded that hypopituitarism is a common complication of TBI and might contribute to morbidity and poor recovery after brain injury (25). However, these reviews did not take into account the variability in diagnostic strategies and definitions of pituitary insufficiency. We hypothesized that methodological differences may have contributed, at least in part, to the discrepancies in prevalence rates of hypopituitarism after TBI. Therefore, the aim of our systematic review in **chapter 2** was to critically compare the pituitary function tests, and definitions of hypopituitarism between studies that assessed the long-term outcome of TBI on pituitary function for each pituitary axis.

We found that the reported prevalence rates of pituitary insufficiency indeed vary considerably and that this is associated with major differences in endocrine and analytic methods of assessment en definitions used for the diagnosis hypopituitarism. The studies in the review used different endocrine tests, cut-off values and analytic methods. Moreover, several confounding factors (such as BMI) were not taken into account when assessing the pituitary axes. This is especially of importance for the assessment of the GH axis given the decrease of GH concentration with increasing BMI. This all may result in an overestimation of hypopituitarism following TBI in obese subjects. These discrepancies limit the possibility to compare the results of studies on TBI. Future studies should be designed to ensure a high diagnostic robustness for proper identification of reliable predictors, as the results may be highly dependent on diagnostic pitfalls (26).

Because of the large variations published on prevalence rates reported and the variations in endocrine and analytical methods to assess pituitary functions, we performed a cross-sectional study in the Netherlands in a large cohort of TBI patients evaluated after long-term follow-up (described in **chapter 3**). We included 112 patients with TBI, hospitalized for at least 3 days and duration of follow-up > 1 yr after TBI from 5 (neurosurgical) referral centers. Evaluation of pituitary function included fasting morning hormone measurements and insulin tolerance test (ITT n=90) or, when contraindicated, ACTH-stimulation and/or CRH-stimulation test and a GHRH-arginine test (n=22).

Our study demonstrates that prevalence of hypopituitarism after TBI after long-term follow-up is low. Using a standardized evaluation that included the golden standard tests for the evaluation of GH and cortisol secretory reserves in the majority of the patients, we found a prevalence of any pituitary insufficiency of only 5.4% (severe growth hormone deficiency (2.8%), hypogonadism (0.9%), adrenal insufficiency (1.8%)). This prevalence is much lower compared to the prevalence rates reported in the majority of the previous studies (15–90%)(5–17). This discrepancy might be explained by the use of different endocrine tests and different cut-off values in the previous studies. If possible we used the golden standard test: the insulin tolerance test. In accordance with the data by Klose *et al.* (21), this resulted in lower prevalence rates of GHD and adrenal insufficiency. If ITT was contraindicated, we used

the combined stimulation with GHRH and arginine to assess the GH axis which has been shown to be a good alternative test, provided higher cut-off GH levels are used. As mentioned above, GH secretion decreases with increasing BMI (2–4). We, therefore, used BMI-adjusted cut-off values for the combined stimulation with GHRH and arginine. In addition to differences in endocrine test, the time interval between TBI and endocrine evaluation as well as trauma severity may also affect the reported prevalence rates. Studies have reported that in the acute phase after TBI hormone alterations mimicking pituitary insufficiency can be present (21;27). To avoid this transient effect of TBI, we evaluated patients at least 1 year post TBI. Increased trauma severity increases the risk of pituitary insufficiency. Therefore, we included only patients with more severe trauma. Patients had to be hospitalized for at least 3 days and GCS was evaluated. In contrast to many previous studies, the prevalence of pituitary insufficiency appeared to be low in patients with more severe trauma at least one year after trauma, using these inclusion criteria and golden standard test for pituitary assessment whenever possible and BMI-adjusted cut-off values if necessary.

Our results indicate that consensus for a more uniform endocrine evaluation of pituitary function in general and after TBI in particular is needed. Nonetheless, pituitary failure, even if present after TBI in a very small proportion of patients, is potentially treatable, may be life-saving, and is likely to ameliorate quality of life (7;10).

III. Dynamic tests of pituitary function in other pituitary diseases

Pituitary adenomas can be treated by transsphenoidal surgery (TS), additional radiotherapy and/or medication. Pituitary insufficiency is a complication that can be attributed to the tumor itself (compression), surgery and/or radiotherapy. Therefore, accurate assessment of pituitary function is critical for appropriate management of patients with pituitary adenoma after surgery with or without irradiation.

Endocrine assessment after pituitary surgery

After TS the assessment of the hypothalamic-pituitary adrenal (HPA) axis is of clinical relevance to judge the need for hydrocortisone replacement therapy at discharge. The ITT is the golden standard to evaluate the HPA axis in patients suspected of secondary adrenal insufficiency. Because of contraindications for the induction of hypoglycemia different other dynamic tests of the HPA axis are available such as the metyrapone test, the ACTH stimulation test and the corticotrophin releasing hormone (CRH)-test. In our clinic (from 1990 onwards) adrenal function of patients directly after surgery has been evaluated by stimulation with CRH. Based on the test result it is decided whether the patients were discharged with our without hydrocortisone replacement therapy. Specific data on the clinical applicability of the CRH test directly after TS are hardly available. Therefore, in **chapter 4** we retrospectively evaluated the clinical relevanceof the CRH stimulation test in assessing pituitary adrenal function after TS.

We performed a retrospective chart review of all patients who had been treated by TS in our center. We included a total of 144 non-Cushing patients of whom data were available on postsurgical CRH tests, of whom second (confirmation) tests were also available and who had not been subjected to confounding factors like use of exogenous glucocorticoids, re-operation or postsurgical radiotherapy. Forty-two patients were diagnosed with hypocortisolism of whom 13 (31%) had sufficient adrenal function during follow-up.

A possible explanation for these discrepant results is the use of different cut-off values. For the ITT (golden standard) regularly accepted cut-off values have been defined. However, for the CRH test different cut-off values for peak cortisol responses have been proposed. Because in our center the CRH test is used as a screening test to identify those patients that require hydrocortisone supplementation after TS, we applied a generally accepted stringent criterion of 550 nmol/L (28;29). Aiming for a higher sensitivity will be at the expense of a lower specificity, i.e a greater proportion of patients will be incorrectly diagnosed with adrenal insufficiency.

Another possible explanation is the recovery of preoperative adrenal insufficiency after TS within one year (5;6). This has been described in a study that compared the ITT response at 3 and 12 months after TS. In agreement, we found a normal adrenal function in 8 patients within the first year after surgery who were inititally diagnosed as being adrenal insufficient. This indicates the necessity of an extensive follow-up in patiens after surgery within one year.

A normal function of the HPA axis was assessed in 102 of the 144 patients. However, fourteen of these patients (14%) appeared to have hypocortisolism based on a second test. These discrepant results can be potentially life-threatening because these patients are at risk for adrenal crises. It is possible that additional pituitary insufficiency influenced the test results of these patients. Growth hormone and thyroid hormone deficiency can influence the test results(5;30–32). Moreover, growth hormone replacement therapy in patients with GHD may also play an important role because of the influence of GH on the cortisol metabolism. Growth hormone stimulates 11–β hydroxysteroid dehydrogenase (11βHSD-1), leading to increased cortisol-cortisone conversion (31). The use of GH replacement therapy in GH-deficient patients may therefore unmask cortisol deficiency (30;32).

Based on our results we conclude that the CRH test can be safely used to guide hydrocortisone substitution after TS. Nonetheless, the cortisol response to this test can not reliably predict adrenal function in all patients during longer follow-up after TS. We therefore recommend to perform a second test of pituitary adrenal function during longer follow-up, e.g. 3–6 months after surgery. This approach is not required in patients with an impaired postoperative cortisol response to CRH, who have multiple pituitary insufficiencies.

In **chapter 4** we retrospectively assessed the HPA function in all patients who had been treated by TS in our center, whereas in **chapter 5** we focused on postoperative assessment of HPA function in a specific postoperative group; patients after TS for GH secreting adenomas *i.e.* patients with acromegaly. A recent study by Ronchi and colleagues evaluated the HPA axis in acromegalic patients after TS. They found a remarkably high prevalence of adrenal insufficiency (32%) after TS in these patients. They concluded that the function of the HPA axis may worsen over time and should be carefully monitored by dynamic testing in all acromegalic patients, independently from the type of treatment. This recommendation has obvious implications for the long-term management of non-irradiated patients with acromegaly (33). Therefore, the aim of **chapter 5** was to evaluate the prevalence of adrenal insufficiency during long-term follow-up in our own unselected cohort of consecutive patients in remission of GH excess after transsphenoidal surgery.

We retrospectively reviewed the assessment of corticotrope function in 91 consecutive patients in remission after transsphenoidal surgery using ITT, CRH stimulation, metyrapone test and ACTH stimulation tests. We found insufficient adrenal function in 16 patients (18%) in the early postoperative period, which was transient in 8 but irreversible in 8 other patients within the first year of postoperative follow-up. Therefore, after the first year of follow-up after curative surgery for acromegaly, the prevalence of adrenal insufficiency was only 9%. Late, new-onset adrenal insufficiency developed in only 3 patients, 13, 18 and 24 years after surgery, resp. The incidence rate of late adrenal insufficiency after successful surgery was only 2/1000 person years. After long-term follow-up, with a median duration of 8.1 yr (range 1–31 yr), the prevalence of secondary adrenal insufficiency was 12% in patients in remission after

surgery for acromegaly. Therefore, new-onset adrenal insufficiency after TS for acromegaly is not frequently present. The discrepancies in prevalence with the study by Ronchi *et al.* and our study may be explained by differences in study design and study population but also by patient selection and differences in surgical techniques. We used the golden standard test (ITT) and CRH test in a large whereas Ronchi and colleagues used a low-dose ACTH test in patients (33). Other potential mechanisms of influence may be changed cortisol binding globulin levels (CBG) in acromegaly (31;32;34;35), the presence of postoperative GH deficiency (30;35;36) and the possibility of recovery of preoperative adrenal insufficiency following transsphenoidal surgery (5;6;37), although this is most likely a rare event.

Limitations of our study are the retrospective nature of the study and the fact that patients had been tested by different cortisol stimulation tests and assays. However, this does not affect our conclusions, since the ITT, CRH and metyrapone tests are all accepted tests for the evaluation of HPA function and we have used unchanged cut-off values of cortisol throughout the years.

We propose to repeat dynamic test of HPA function 1 yr post surgery in patients with postoperative HPA insufficiency. Further research is required to assess whether yearly basal cortisol values may suffice to monitor adrenal function in asymptomatic patients. However, in case of low basal cortisol levels, symptoms suggestive of corticotrope insufficiency or progressive impairment of other pituitary functions, additional dynamic testing of the HPA axis should be performed.

Endocrine assessment following cranial radiotherapy

Patients with nonpituitary intracranial and/or nasopharyngeal tumors are frequently treated by radiotherapy, in which the pituitary gland is involved in the radiation field. These patients are at risk for pituitary insufficiency. This is well described in children treated with cranial radiotherapy (38–46), but the assessment of pituitary function during long term follow-up has not been implemented in the guidelines of patients treated by cranial radiotherapy for nonpituitary tumors. To assess the prevalence of pituitary insufficiencies after cranial radiotherapy in these patients, we performed a systemic literature search and meta-analysis

focusing on the prevalence of pituitary dysfunction in adult patients treated with radiotherapy for nonpituitary tumors, which is described in **chapter 6**.

Our review ultimately included 18 studies (n=813) evaluating patients treated for nasopharyngeal cancer or intracerebral tumors (47–64). There were considerable variations in the reported prevalence rates of hypopituitarism after cranial radiotherapy, ranging from hardly any effect on pituitary function to almost 100% of the patients being affected. These variations may be associated with differences in radiotherapeutic techniques, study design, time of evaluation, patient selection and differences in endocrine evaluation. The majority of patients was not evaluated by pituirary stimulation tests. If stimulation tests had been used, different cut-off values and diagnostic criteria were used. Our meta-analysis showed that any hypopituitarism is present in approximately two thirds of all adult patients previously treated by cranial radiotherapy (0.66, CI 0.55–0.76). The prevalence of growth hormone deficiency was 0.45 (CI 0.33–0.57), of LH and FSH 0.3 (CI 0.23–0.37), of TSH 0.25 (CI 0.16–0.37), and of ACTH 0.22 (CI 0.15–0.3), respectively. The prevalence of hyperprolactinemia was 0.34 (CI 0.15–0.6) There were no differences between the effects of radiotherapy for nasopharyngeal versus for intracerebral tumors.

Based on these data we conclude that hypopituitarism is rather prevalent in adult patients after cranial radiotherapy for nonpituitary tumors. Considering this high prevalence of hypopituitarism, the evaluation of pituitary function should be included in the guidelines of long-term follow-up of all patients treated by cranial radiotherapy.

IV. Treatment of GHD

When growth hormone deficiency is considered, the therapeutical implications should be carefully evaluated, especially in elderly subjects in whom normal growth hormone secretion and IGF-I levels are low compared to young adults and GH and IGF-I levels overlap between normal and growth hormone deficient subjects.

In **chapter 7**, we performed a systematic review, to critically assess the available literature on the evidence of clinical efficacy of rhGH in elderly patients with GHD. We ultimately included only 11 eligible studies with a total of 534 patients (65–78). The studies show that there are undeniable effects of rhGH substitution in elderly subjects with GHD for some, but not all, parameters. RhGH treatment unequivocally positively affects total and LDL cholesterol levels and QoL parameters. However, there is controversy on the effects on other cardiovascular risk factors, including insulin, HDL cholesterol, BP and BC, whereas rhGH therapy does not improve plasma triglyceride levels. Moreover, treatment with rhGH did not improve BMD in elderly subjects with GHD. Studies in octogenarians have not been performed. Finally, there are no data on the effects of rhGH on clinically relevant end points, like cardiovascular disease or fractures.

Several factors should be taken into account in the assessment of the effects of rhGH therapy in elderly subjects. With increasing age GH secretion decreases. This decrease in GH levels may affect the response to stimulation tests and, therefore, affect the cut-off values of the GH stimulation tests. Studies using the ITT and GHRH-arginine stimulation test have been performed in these patients with various results. Some studies show a lower peak of GH response in elderly compared to younger patients (79;80), whereas other studies show no differences (81). Nonetheless, the omission to reduce the cut-off values of GH stimulation tests in aging subjects might result in an erroneous diagnosis of GHD in at least some of these subjects. The extent to which this may have affected the conclusions is uncertain at present.

The decline of GH levels during aging is associated with a decline in IGF-I levels. Therefore, age-adjusted IGF-I SD scores are necessary to enable to assess the treatment response to rhGH. In this respect, there were methodological differences between the included studies, which may have affected the relation between physiological rhGH replacement and responses in elderly subjects. Moreover, from an evolutionary perspective, the natural decrease of GH and IGF-I levels during normal aging may even be beneficial. In animal models of decreased GH-IGF-I function longevity was increased (82–89). Accordingly, it is presently not straightforward that all elderly subjects with GHD should be treated unconditionally.

In conclusion, only a small number of randomized placebo-controlled trials have assessed the beneficial effects of rhGH therapy in elderly with GHD. These studies show relatively limited effects. Therefore, the question remains whether the treatment with rhGH is clinically relevant in elderly patients with GHD. There are no data whatsoever on the effects of rhGH in octogenarians with GHD.

V. Concluding remarks

The conclusions of the studies described in this thesis can be summarized as follows:

Pituitary function after TBI

There is a wide variation in the reported prevalence rates of hypopituitarism after TBI. This is at least in part caused by differences in definitions, endocrine assessments of hypopituitarism, and confounding factors. These methodological issues prohibit simple generalizations of results of original studies on TBI-associated hypopituitarism in the perspective of meta-analyses or reviews.

The prevalence of hypopituitarism during long-term follow-up after TBI is most likely very low, if stringent criteria and appropriate pituitary tests are used. The reported prevalence rates of pituitary insufficiency after TBI are most likely overestimated.

Pituitary function after transsphenoidal surgery

The CRH test is a valuable tool to define clinically relevant cortisol deficiency immediately after pituitary surgery. This test can be safely used to define hydrocortisone dependency at discharge until a second test is performed.

In patients with acromegaly cured by transsphenoidal surgery, the prevalence of adrenal insufficiency very low: 9% one year after surgery and only 2/1000 person-years in patients in long term remission after surgery. Therefore, development of late-onset adrenal insufficiency is a

very infrequent complication in patients with acromegaly in remission after transsphenoidal surgery only.

Pituitary function after cranial radiotherapy

Hypopituitarism is very prevalent in adult patients after cranial radiotherapy for nonpituitary tumors. Therefore, all patients treated by cranial radiotherapy should have structured periodical assessment of pituitary function during follow-up. This should be implemented in the guidelines of follow-up of these patients.

Pituitary function in elderly subjects

Recombinant GH replacement in elderly subjects with GHD decreases LDL cholesterol levels and improves QoL, but the effects on other parameters are not unequivocal. There are no data on the efficacy and safety of rhGH treatment in octogenarians with GHD. There are no data on clinically relevant endpoints like cardiovascular disease or fractures.

References

1. van Aken MO, Lamberts SW 2005 Diagnosis and treatment of hypopituitarism: an update. Pituitary 8:183–191
2. Iranmanesh A, Lizarralde G, Veldhuis JD 1991 Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab 73:1081–1088
3. Veldhuis JD, Liem AY, South S, Weltman A, Weltman J, Clemmons DA, Abbott R, Mulligan T, Johnson ML, Pincus S, . 1995 Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay. J Clin Endocrinol Metab 80:3209–3222
4. Veldhuis JD, Roelfsema F, Keenan DM, Pincus S 2011 Gender, age, body mass index, and IGF-I individually and jointly determine distinct GH dynamics: analyses in one hundred healthy adults. J Clin Endocrinol Metab 96:115–121
5. Arafah BM 1986 Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 62:1173–1179
6. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F 1999 Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab 84:3696–3700
7. Blair JC 2010 Prevalence, natural history and consequences of posttraumatic hypopituitarism: a case for endocrine surveillance. Br J Neurosurg 24:10–17
8. Fleminger S, Ponsford J 2005 Long term outcome after traumatic brain injury. BMJ 331:1419–1420
9. van Aken MO, Lamberts SW 2005 Diagnosis and treatment of hypopituitarism: an update. Pituitary 8:183–191
10. Maric NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M, Popovic V 2010 Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. J Endocrinol Invest 33:770–775
11. Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ 2001 Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab 86:2752–2756
12. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C 2000 Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 93:743–752

13. Bondanelli M, De ML, Ambrosio MR, Monesi M, Valle D, Zatelli MC, Fusco A, Bianchi A, Farneti M, gli Uberti EC 2004 Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 21:685–696
14. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, Thompson CJ 2004 Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 89:4929–4936
15. Aimaretti G, Ambrosio MR, Di SC, Gasperi M, Cannavo S, Scaroni C, Fusco A, Del MP, De ME, Faustini-Fustini M, Grimaldi F, Logoluso F, Razzore P, Rovere S, Benvenga S, gli Uberti EC, De ML, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E 2005 Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12–month study. J Clin Endocrinol Metab 90:6085–6092
16. Popovic V, Pekic S, Pavlovic D, Maric N, Jasovic-Gasic M, Djurovic B, Medic SM, Zivkovic V, Stojanovic M, Doknic M, Milic N, Djurovic M, Dieguez C, Casanueva FF 2004 Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. J Endocrinol Invest 27:1048–1054
17. Leal-Cerro A, Flores JM, Rincon M, Murillo F, Pujol M, Garcia-Pesquera F, Dieguez C, Casanueva FF 2005 Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. Clin Endocrinol (Oxf) 62:525–532
18. Schneider HJ, Schneider M, Saller B, Petersenn S, Uhr M, Husemann B, von RF, Stalla GK 2006 Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. Eur J Endocrinol 154:259–265
19. Tanriverdi F, Senyurek H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F 2006 High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. J Clin Endocrinol Metab 91:2105–2111
20. Herrmann BL, Rehder J, Kahlke S, Wiedemayer H, Doerfler A, Ischebeck W, Laumer R, Forsting M, Stolke D, Mann K 2006 Hypopituitarism following severe traumatic brain injury. Exp Clin Endocrinol Diabetes 114:316–321
21. Klose M, Juul A, Poulsgaard L, Kosteljanetz M, Brennum J, Feldt-Rasmussen U 2007 Prevalence and predictive factors of post-traumatic hypopituitarism. Clin Endocrinol (Oxf) 67:193–201
22. Bushnik T, Englander J, Katznelson L 2007 Fatigue after TBI: association with neuroendocrine abnormalities. Brain Inj 21:559–566
23. Wachter D, Gundling K, Oertel MF, Stracke H, Boker DK 2009 Pituitary insufficiency after traumatic brain injury. J Clin Neurosci 16:202–208
24. Tanriverdi F, Ulutabanca H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F 2008 Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. Clin Endocrinol (Oxf) 68:573–579

25. Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A 2007 Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 298:1429–1438
26. Klose M, Feldt-Rasmussen U 2008 Does the type and severity of brain injury predict hypothalamo-pituitary dysfunction? Does post-traumatic hypopituitarism predict worse outcome? Pituitary 11:255–261
27. Klose M, Juul A, Struck J, Morgenthaler NG, Kosteljanetz M, Feldt-Rasmussen U 2007 Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study. Clin Endocrinol (Oxf) 67:598–606
28. Trainer PJ, Faria M, Newell-Price J, Browne P, Kopelman P, Coy DH, Besser GM, Grossman AB 1995 A comparison of the effects of human and ovine corticotropin-releasing hormone on the pituitary-adrenal axis. J Clin Endocrinol Metab 80:412–417
29. Lytras N, Grossman A, Perry L, Tomlin S, Wass JA, Coy DH, Schally AV, Rees LH, Besser GM 1984 Corticotrophin releasing factor: responses in normal subjects and patients with disorders of the hypothalamus and pituitary. Clin Endocrinol (Oxf) 20:71–84
30. Giavoli C, Libe R, Corbetta S, Ferrante E, Lania A, Arosio M, Spada A, Beck-Peccoz P 2004 Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. J Clin Endocrinol Metab 89:5397–5401
31. Moore JS, Monson JP, Kaltsas G, Putignano P, Wood PJ, Sheppard MC, Besser GM, Taylor NF, Stewart PM 1999 Modulation of 11beta-hydroxysteroid dehydrogenase isozymes by growth hormone and insulin-like growth factor: in vivo and in vitro studies. J Clin Endocrinol Metab 84:4172–4177
32. Rodriguez-Arnao J, Perry L, Besser GM, Ross RJ 1996 Growth hormone treatment in hypopituitary GH deficient adults reduces circulating cortisol levels during hydrocortisone replacement therapy. Clin Endocrinol (Oxf) 45:33–37
33. Ronchi CL, Ferrante E, Rizzo E, Giavoli C, Verrua E, Bergamaschi S, Lania AG, Beck-Peccoz P, Spada A 2008 Long-term basal and dynamic evaluation of hypothalamic-pituitary-adrenal (HPA) axis in acromegalic patients. Clin Endocrinol (Oxf) 69:608–612
34. Weaver JU, Thaventhiran L, Noonan K, Burrin JM, Taylor NF, Norman MR, Monson JP 1994 The effect of growth hormone replacement on cortisol metabolism and glucocorticoid sensitivity in hypopituitary adults. Clin Endocrinol (Oxf) 41:639–648
35. Tschop M, Lahner H, Feldmeier H, Grasberger H, Morrison KM, Janssen OE, Attanasio AF, Strasburger CJ 2000 Effects of growth hormone replacement therapy on levels of cortisol and cortisol-binding globulin in hypopituitary adults. Eur J Endocrinol 143:769–773
36. Isidori AM, Kaltsas GA, Perry L, Burrin JM, Besser GM, Monson JP 2003 The effect of growth hormone replacement therapy on adrenal androgen secretion in adult onset hypopituitarism. Clin Endocrinol (Oxf) 58:601–611

37. Berg C, Meinel T, Lahner H, Mann K, Petersenn S 2010 Recovery of pituitary function in the late-postoperative phase after pituitary surgery: results of dynamic testing in patients with pituitary disease by insulin tolerance test 3 and 12 months after surgery. Eur J Endocrinol 162:853–859
38. Alvarez JA, Scully RE, Miller TL, Armstrong FD, Constine LS, Friedman DL, Lipshultz SE 2007 Long-term effects of treatments for childhood cancers. Curr Opin Pediatr 19:23–31
39. Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, Rubin P 1993 Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 328:87–94
40. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL 2006 Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572–1582
41. Schmiegelow M, Lassen S, Poulsen HS, Feldt-Rasmussen U, Schmiegelow K, Hertz H, Muller J 2000 Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. Clin Endocrinol (Oxf) 53:191–197
42. Shalet SM, Beardwell CG, Jones PH, Pearson D 1976 Growth hormone deficiency after treatment of acute leukaemia in children. Arch Dis Child 51:489–493
43. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Poulsen HS, Muller J 2003 A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. J Clin Endocrinol Metab 88:136–140
44. Shalet SM, Beardwell CG, Morris-Jones P, Bamford FN, Ribeiro GG, Pearson D 1976 Growth hormone deficiency in children with brain tumors. Cancer 37:1144–1148
45. Shalet SM, Beardwell CG, MacFarlane IA, Jones PH, Pearson D 1977 Endocrine morbidity in adults treated with cerebral irradiation for brain tumours during childhood. Acta Endocrinol (Copenh) 84:673–680
46. Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, Stovall M, Yasui Y, Nicholson HS, Wolden S, McNeil DE, Mertens AC, Robison LL 2003 Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 97:663–673
47. Snyers A, Janssens GO, Twickler MB, Hermus AR, Takes RP, Kappelle AC, Merkx MA, Dirix P, Kaanders JH 2009 Malignant tumors of the nasal cavity and paranasal sinuses: long-term outcome and morbidity with emphasis on hypothalamic-pituitary deficiency. Int J Radiat Oncol Biol Phys 73:1343–1351
48. Bhandare N, Kennedy L, Malyapa RS, Morris CG, Mendenhall WM 2008 Hypopituitarism after radiotherapy for extracranial head and neck cancers. Head Neck 30:1182–1192
49. Lam KS, Tse VK, Wang C, Yeung RT, Ho JH 1991 Effects of cranial irradiation on hypothalamic-pituitary function--a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med 78:165–176

50. Woo E, Lam K, Yu YL, Ma J, Wang C, Yeung RT 1988 Temporal lobe and hypothalamic-pituitary dysfunctions after radiotherapy for nasopharyngeal carcinoma: a distinct clinical syndrome. J Neurol Neurosurg Psychiatry 51:1302–1307
51. Samaan NA, Schultz PN, Yang KP, Vassilopoulou-Sellin R, Maor MH, Cangir A, Goepfert H 1987 Endocrine complications after radiotherapy for tumors of the head and neck. J Lab Clin Med 109:364–372
52. Lam KS, Ho JH, Lee AW, Tse VK, Chan PK, Wang C, Ma JT, Yeung RT 1987 Symptomatic hypothalamic-pituitary dysfunction in nasopharyngeal carcinoma patients following radiation therapy: a retrospective study. Int J Radiat Oncol Biol Phys 13:1343–1350
53. Lam KS, Wang C, Yeung RT, Ma JT, Ho JH, Tse VK, Ling N 1986 Hypothalamic hypopituitarism following cranial irradiation for nasopharyngeal carcinoma. Clin Endocrinol (Oxf) 24:643–651
54. Huang KE 1979 Assessment of hypothalamic-pituitary function in women after external head irradiation. J Clin Endocrinol Metab 49:623–627
55. Rosenthal MB, Goldfine ID 1976 Primary and secondary hypothyroidism in nasopharyngeal carcinoma. JAMA 236:1591–1593
56. Samaan NA, Bakdash MM, Caderao JB, Cangir A, Jesse RH, Jr., Ballantyne AJ 1975 Hypopituitarism after external irradiation. Evidence for both hypothalamic and pituitary origin. Ann Intern Med 83:771–777
57. Schneider HJ, Rovere S, Corneli G, Croce CG, Gasco V, Ruda R, Grottoli S, Stalla GK, Soffietti R, Ghigo E, Aimaretti G 2006 Endocrine dysfunction in patients operated on for nonpituitary intracranial tumors. Eur J Endocrinol 155:559–566
58. Agha A, Sherlock M, Brennan S, O'Connor SA, O'Sullivan E, Rogers B, Faul C, Rawluk D, Tormey W, Thompson CJ 2005 Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab 90:6355–6360
59. Johannesen TB, Lien HH, Hole KH, Lote K 2003 Radiological and clinical assessment of long-term brain tumour survivors after radiotherapy. Radiother Oncol 69:169–176
60. Popovic V, Pekic S, Golubicic I, Doknic M, Dieguez C, Casanueva FF 2002 The impact of cranial irradiation on GH responsiveness to GHRH plus GH-releasing peptide-6. J Clin Endocrinol Metab 87:2095–2099
61. Taphoorn MJ, Heimans JJ, van d, V, Karim AB 1995 Endocrine functions in long-term survivors of low-grade supratentorial glioma treated with radiation therapy. J Neurooncol 25:97–102
62. Constine LS, Rubin P, Woolf PD, Doane K, Lush CM 1987 Hyperprolactinemia and hypothyroidism following cytotoxic therapy for central nervous system malignancies. J Clin Oncol 5:1841–1851
63. Mechanick JI, Hochberg FH, LaRocque A 1986 Hypothalamic dysfunction following whole-brain irradiation. J Neurosurg 65:490–494
64. Harrop JS, Davies TJ, Capra LG, Marks V 1976 Hypothalamic-pituitary function following successful treatment of intracranial tumours. Clin Endocrinol (Oxf) 5:313–321

65. De ML, Mancini A, Giampietro A, Gentilella R, Bianchi A, Perrelli M, Vezzosi C, Milardi D, Fusco A, Valle D, Bernabei R 2002 GH deficiency syndrome in elderly patients. J Endocrinol Invest 25:40–41
66. Elgzyri T, Castenfors J, Hagg E, Backman C, Thoren M, Bramnert M 2004 The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. Clin Endocrinol (Oxf) 61:113–122
67. Feldt-Rasmussen U, Wilton P, Jonsson P 2004 Aspects of growth hormone deficiency and replacement in elderly hypopituitary adults. Growth Horm IGF Res 14 Suppl A:S51–S58
68. Fernholm R, Bramnert M, Hagg E, Hilding A, Baylink DJ, Mohan S, Thoren M 2000 Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. J Clin Endocrinol Metab 85:4104–4112
69. Franco C, Johannsson G, Bengtsson BA, Svensson J 2006 Baseline characteristics and effects of growth hormone therapy over two years in younger and elderly adults with adult onset GH deficiency. J Clin Endocrinol Metab 91:4408–4414
70. Gill MS, Toogood AA, Jones J, Clayton PE, Shalet SM 1999 Serum leptin response to the acute and chronic administration of growth hormone (GH) to elderly subjects with GH deficiency. J Clin Endocrinol Metab 84:1288–1295
71. Gotherstrom G, Bengtsson BA, Sunnerhagen KS, Johannsson G, Svensson J 2005 The effects of five-year growth hormone replacement therapy on muscle strength in elderly hypopituitary patients. Clin Endocrinol (Oxf) 62:105–113
72. Gotherstrom G, Elbornsson M, Stibrant-Sunnerhagen K, Bengtsson BA, Johannsson G, Svensson J 2010 Muscle strength in elderly adults with GH deficiency after 10 years of GH replacement. Eur J Endocrinol 163:207–215
73. Koltowska-Haggstrom M, Mattsson AF, Shalet SM 2009 Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations. Eur J Endocrinol 161 Suppl 1:S51–S64
74. Monson JP, Abs R, Bengtsson BA, Bennmarker H, Feldt-Rasmussen U, Hernberg-Stahl E, Thoren M, Westberg B, Wilton P, Wuster C 2000 Growth hormone deficiency and replacement in elderly hypopituitary adults. KIMS Study Group and the KIMS International Board. Pharmacia and Upjohn International Metabolic Database. Clin Endocrinol (Oxf) 53:281–289
75. Monson JP, Jonsson P 2003 Aspects of growth hormone (GH) replacement in elderly patients with GH deficiency: data from KIMS. Horm Res 60:112–120
76. Sathiavageeswaran M, Burman P, Lawrence D, Harris AG, Falleti MG, Maruff P, Wass J 2007 Effects of GH on cognitive function in elderly patients with adult-onset GH deficiency: a placebo-controlled 12-month study. Eur J Endocrinol 156:439–447
77. Toogood AA, Shalet SM 1999 Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease: a dose-finding study. J Clin Endocrinol Metab 84:131–136

78. White HD, Ahmad AM, Durham BH, Patwala A, Whittingham P, Fraser WD, Vora JP 2005 Growth hormone replacement is important for the restoration of parathyroid hormone sensitivity and improvement in bone metabolism in older adult growth hormone-deficient patients. J Clin Endocrinol Metab 90:3371–3380
79. Colao A, Di SC, Savastano S, Rota F, Savanelli MC, Aimaretti G, Lombardi G 2009 A reappraisal of diagnosing GH deficiency in adults: role of gender, age, waist circumference, and body mass index. J Clin Endocrinol Metab 94:4414–4422
80. Eskes SA, Tomasoa NB, Endert E, Geskus RB, Fliers E, Wiersinga WM 2009 Establishment of reference values for endocrine tests. Part VII: growth hormone deficiency. Neth J Med 67:127–133
81. Finucane FM, Liew A, Thornton E, Rogers B, Tormey W, Agha A 2008 Clinical insights into the safety and utility of the insulin tolerance test (ITT) in the assessment of the hypothalamo-pituitary-adrenal axis. Clin Endocrinol (Oxf) 69:603–607
82. Bartke A, Brown-Borg H 2004 Life extension in the dwarf mouse. Curr Top Dev Biol 63:189–225
83. Bartke A 2008 Growth hormone and aging: a challenging controversy. Clin Interv Aging 3:659–665
84. Bonkowski MS, Pamenter RW, Rocha JS, Masternak MM, Panici JA, Bartke A 2006 Long-lived growth hormone receptor knockout mice show a delay in age-related changes of body composition and bone characteristics. J Gerontol A Biol Sci Med Sci 61:562–567
85. Brosnahan MM, Paradis MR 2003 Assessment of clinical characteristics, management practices, and activities of geriatric horses. J Am Vet Med Assoc 223:99–103
86. Coschigano KT, Holland AN, Riders ME, List EO, Flyvbjerg A, Kopchick JJ 2003 Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. Endocrinology 144:3799–3810
87. Greer KA, Canterberry SC, Murphy KE 2007 Statistical analysis regarding the effects of height and weight on life span of the domestic dog. Res Vet Sci 82:208–214
88. Patronek GJ, Waters DJ, Glickman LT 1997 Comparative longevity of pet dogs and humans: implications for gerontology research. J Gerontol A Biol Sci Med Sci 52:B171–B178
89. Rollo CD 2002 Growth negatively impacts the life span of mammals. Evol Dev 4:55–61