Hypopituitarism : clinical assessment in different conditions

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Voor Papa en Mama,
Aan mijn lieve Oma

Hypopituitarism

Clinical assessment in different conditions

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Contents

Chapter 1

General introduction and outline of this thesis

Contents

I. General introduction

The pituitary gland is the master regulator of the endocrine system. Different pathophysiological conditions can affect the function of the pituitary gland and, consequently, endocrine homeostasis. The evaluation of pituitary function is therefore complex and the different tools that have become available to evaluate pituitary function only provide limited information of different aspects of hormone secretion. In this thesis, several difficulties encountered in establishing a diagnosis of pituitary insufficiency are studied in different pathophysiological conditions.

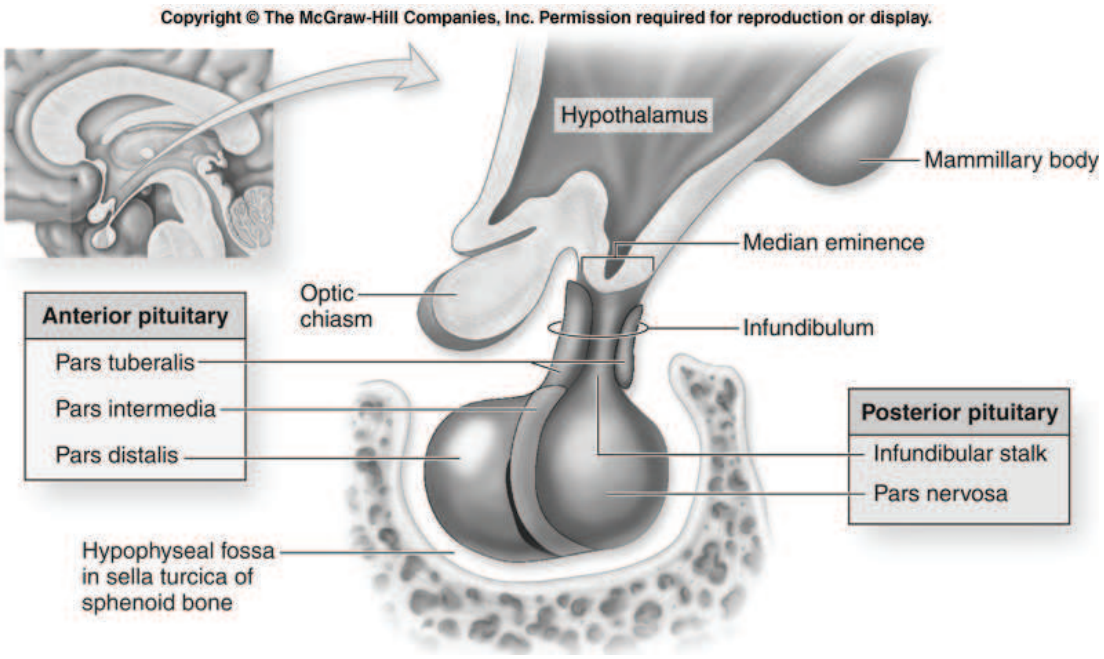

Figure 1. The pituitary gland

II. The pituitary gland

Anatomy and Physiology

The pituitary gland is a small gland located at the base of the skull in a socket of sphenoid bone, called the sella turcica. The gland consists of two lobes, the anterior lobe (or adenohypophysis; 80%), and a posterior lobe (neurohypophysis; 20%) (Figure 1).

Together with the hypothalamus, the pituitary controls the function of different endocrine glands (*i.e.* thyroid, adrenal and reproductive glands) (1). The hypothalamus receives signals from upper corticol inputs and the environment (such as light and temperature) and, in turn, delivers signals to the pituitary gland (*i.e.* regulating the endocrine system). Hormones released by the pituitary gland influence the endocrine systems in the body and also have a feedback on the hypothalamus.

The communication between the hypothalamus and anterior pituitary is via the portal system that runs through the pituitary stalk. Hormones released by the hypothalamus are delivered to the anterior pituitary through these vessels and reach the anterior lobe through a dense capillary network. The communication with the posterior gland is via axons and nerve terminals of larger neurons that originate from within the hypothalamus. The hormones produced in these neurons, arginine-vasopressin and oxytocin, are released directly from the posterior pituitary into the systemic circulation.

The anterior pituitary is controlled by specific hypothalamic hormones: thyrotropin releasing hormone (TRH), gonadotropin releasing hormone (GnRH), corticotropin releasing hormone (CRH), growth hormone releasing hormone (GHRH), and somatostatin, that bind specific transmembrane receptors expressed in different anterior pituitary cells. These anterior pituitary cells are classified by their specific secretory products: somatotrophs (GH-secreting cells, expressing the GHRH and somatostatin receptor; 50%), lactotrophs (PRL-secreting cells, expressing the prolactin receptor; 10–25%), corticotrophs (cells secreting ACTH,

expressing the CRH receptor; 15–20%), thyrotrophs (cells secreting TSH, expressing the TRH receptor; 10%), and gonadotrophs (LH and FSH secreting cells, expressing the GnRH receptor; 10–15%) (2).

1. Regulation and secretion of growth hormone and IGF-I

The regulation of growth hormone (GH) secretion is complex and involves many stimulatory and inhibitory hypothalamic peptides. However, the two most important components are growth hormone-releasing hormone (GHRH), which stimulates the somatotrophic cells, and somatostatin (SST) which inhibits GH release (2). The secretion of GH is also affected by factors such as nutrition (increased in fasting, stimulated by high protein meals and inhibit by hyperglycemia and leptin), other hormones (stimulated by estrogens and inhibited by glucocorticoid excess), neuropeptides, neurotransmitters and opiates (2–4).

The secretion of GH is pulsatile with undetectable serum GH levels between the pulses. In normal subjects the 24-hour profile of plasma GH levels consists of stable low levels interrupted by bursts of secretion (Figure 2 and 3). The major determinant of GH secretion in humans is sleep. GH secretion is lower in elderly and obese subjects and there are sex-specific differences in GH pulse amplitude and mass (5;6). The age-associated changes in the GH profile include a reduction in GH secretory burst frequency, the half life of endogenous GH and the daily secretory rate (7). In obese subjects decreased GH concentrations result from both diminished pulsatile GH secretion and accelerated metabolic clearance (4;8).

In the liver, GH stimulates the production of insulin-like growth factor (IGF-I). The primary function of GH is promotion of linear growth in children by acting directly and indirectly (via the synthesis of IGF-I which mediates most of the peripheral actions of GH) on the epiphyseal plates of long bones. Whereas GH and IGF-I have synergistic effects on linear and organ growth by their control of mitogenesis and apoptosis and on glomerular filtration rate, their metabolic actions are opposing: GH stimulates lipolysis and reduces insulin sensitivity, IGF-I is anti-lipolytic and ameliorates insulin sensitivity (9;10).

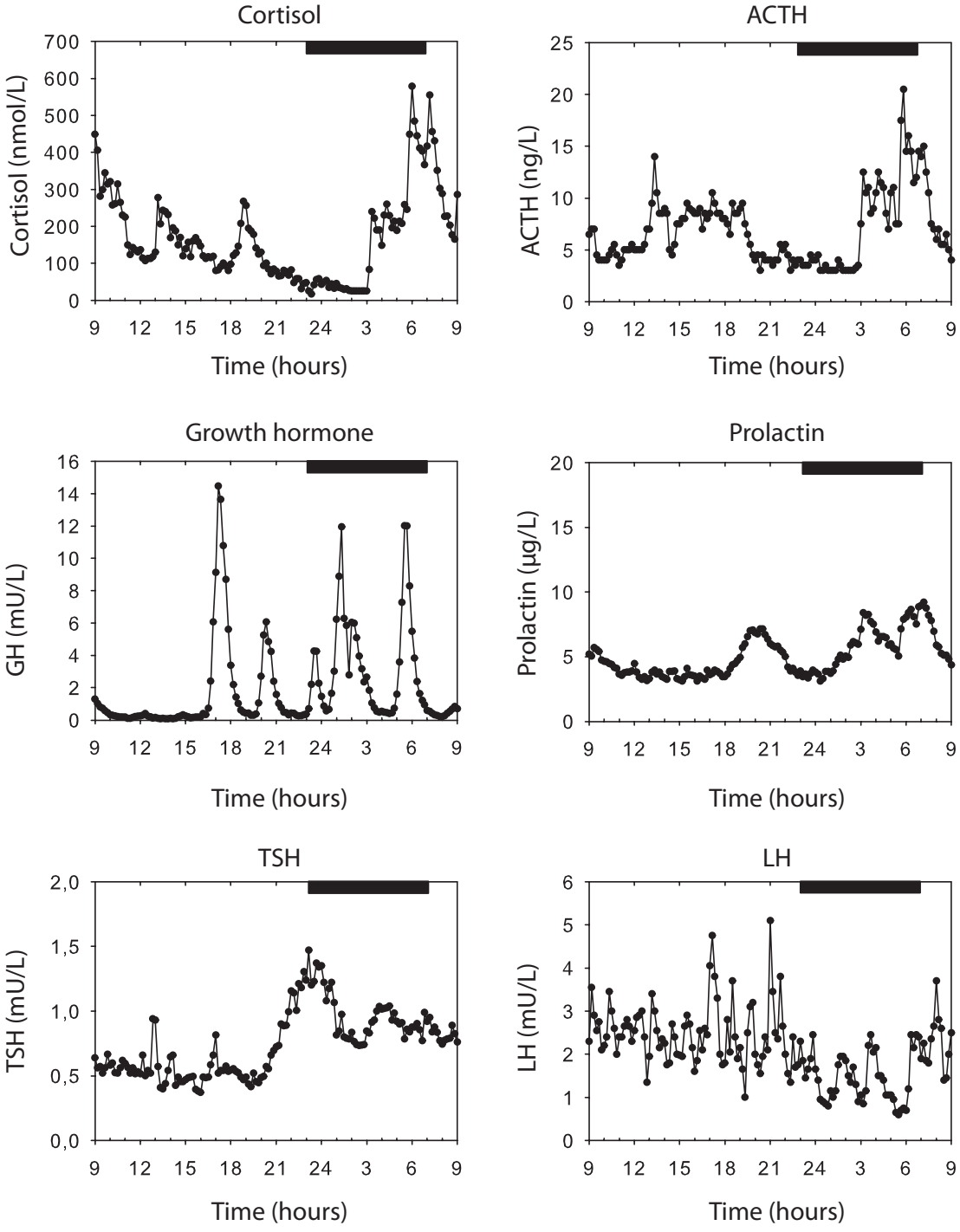

Figure 2. Plasma hormone concentration profiles of a 33 year-old healthy female volunteer. Blood samples were taken at 10 min intervals during 24 hours. The black bar in the top of the panels indicate the period with lights off. Note the diurnal and the pulsatile characteristics of each hormone. *(The figure was provided by Dr. F. Roelfsema, Leiden University.)*

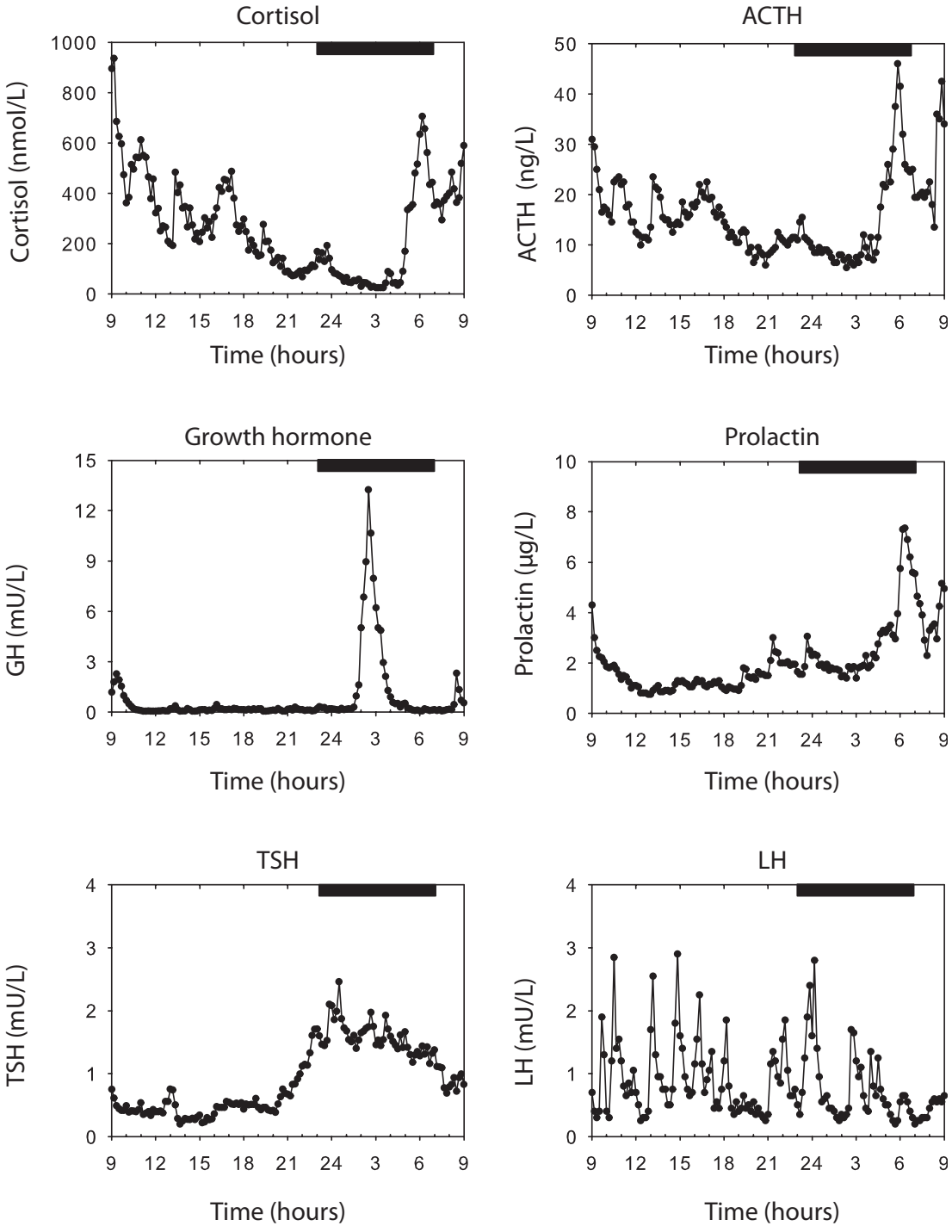

Figure 3. Plasma hormone concentration profiles of a 37 year-old healthy male volunteer. Blood samples were taken at 10 min intervals during 24 hours. The black bar in the top of the panels indicate the period with lights off. Note the diurnal and the pulsatile characteristics of each hormone. *(The figure was provided by Dr. F. Roelfsema, Leiden University.)*

2. Regulation of ACTH and cortisol secretion

The secretion of corticotropin (ACTH) and cortisol is regulated by hormonal interactions between the hypothalamus, pituitary, and adrenal glands. The secretion of hypothalamic corticotropin-releasing hormone (CRH) is regulated mainly by hippocampal neurons that express both receptors for cortisol, the mineralocorticoid- and glucocorticoid receptor. In addition the secretion is influenced by the circadian pacemaker and stress (2;11). CRH regulates the secretion of ACTH by the pituitary gland, which is potentiated by arginine-vasopressin. Subsequently ACTH binds to its receptor on the adrenal cortex to stimulate the secretion of cortisol and other steroids. The negative feedback loop is completed by the inhibitory effect of cortisol on CRH and ACTH synthesis and secretion (11).

Pulsatile secretion and circadian rhythm

ACTH is secreted in brief episodic bursts resulting in a diurnal rhythm of ACTH secretion with a concordant diurnal secretion of cortisol from the adrenal cortex (12;13). Plasma ACTH and serum cortisol concentrations are highest early in the morning at time of awakening. During the day plasma cortisol levels fall resulting in low levels in the late afternoon and evening with a nadir one or two hours after sleep onset (Figure 2 and 3) (11;14;15).

Stress-induced secretion

The HPA axis is activated both by physical and psychological stressors, resulting in increased plasma ACTH and cortisol concentrations. Physical stressors include severe trauma, like burns (16;17), or illnesses, major surgery (18;19), but also hypoglycemia (20;21), hypotension, exercise (22), and cold exposure (23).

Negative feedback inhibition by glucocorticoids

Both endogenous and exogenous glucocorticoids have a negative feedback on ACTH secretion which occurs at both the hypothalamic (CRH suppression) and pituitary (ACTH suppression) levels. This leads to atrophy of the adrenal glands resulting in loss of cortisol secretory capacity (24). The degree of probably depends upon the dose, potency and duration of action of the glucocorticoid, and the time of its administration (25–29). The shorter the interval between the

administration of glucocorticoid and the normal early morning peak of ACTH secretion, the greater the suppressive effect of the glucocorticoid. The duration of suppression is increased by higher doses and longer-acting glucocorticoids. After withdrawal of chronic administration of high doses of glucocorticoid, suppression of the hypothalamic-pituitary-adrenal axis may persist for weeks but may even persist for many years.

3. Regulation and secretion of thyroid hormone, gonadotropins and prolactin

The hypothalamus-pituitary thyroidal axis regulates the production of thyroid hormone by the thyroid gland. The hypothalamus produces thyroptropin releasing hormone (TRH) which stimulates the pituitary gland to secrete thyrotropin (TSH). TSH stimulates the synthesis of the thyroid hormones (thyroxine (T_4) and triiodothyronine (T_3)) by binding to the TSH receptors on the thyroid cells. The response of TSH to TRH is, in turn, modulated by the circulating concentrations of T_3 and T_4. High serum levels of T_3 and T_4 inhibit and low levels stimulate TSH synthesis (2).

The reproductive axis is controlled by periodic pulsatile release of the hypothalamic gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary to secrete the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The production of steroid hormones (including estradiol, progesterone and testosterone), as well as other factors such as inhibin, activin and insulin-like growth factor-I (IGF-I) are induced by the gonadotropins. The circulating sex steroids have a positive as well as negative feedback on GnRH and thereby also influence LH and FSH concentrations.

The function of LH in men is to stimulate testosterone production from interstitial cells of the testes (Leydig cells) and FSH is required for spermatogenesis. In women, LH is critical for ovulation and maintenance of the corpus luteum, whereas FSH promotes follicular development (2).

The main physiological role of prolactin (PRL) is for nursing. The hypothalamic control of PRL secretion is predominantly inhibitory, and dopamine is the most important inhibitory factor. TRH is a potent prolactin-releasing factor (2).

III. Pituitary insufficiency

Hypopituitarism refers to decreased secretion of pituitary hormones, which can result from diseases of the pituitary gland and/or the hypothalamus, which cause diminished secretion of hypothalamic releasing hormones, thereby reducing secretion of the corresponding pituitary hormones. Pituitary insufficiency can be congenital (which will not be further addressed in this thesis) or acquired.

Pituitary adenomas and its treatment

A common cause of pituitary dysfunction is the presence of a pituitary adenoma. Macro-adenomas (> 10 mm) can be associated with pituitary insufficiency, with one or more anterior pituitary hormone deficiencies (30–32). In the presence of macroadenomas, hypopituitarism may result from compression of the rest of the pituitary and/or compression of the portal vessels in the pituitary stalk, secondary to either the expanding tumor mass or directly by increased intra-sellar pressure (30). Conversely, reduction of tumor mass by surgery and/or medication relieves the pressure and may restore pituitary function.

In pituitary surgery the surgeon attempts to preserve the adjacent normal pituitary tissue. However, if the surgeon is not able to visually distinguish the normal pituitary tissue from the adenoma, the normal tissue may be damaged, resulting in pituitary deficiency (33;34).

Radiation of pituitary adenomas, usually to prevent regrowth of residual tissue after surgery or to control excessive GH or ACTH secretion, also exposes the nonadenomatous pituitary and the hypothalamus to irradiation resulting in pituitary insufficiency (35;36). Not only patients with pituitary tumors but also patients treated with radiotherapy for suprasellar lesions, primary brain tumors, nasopharyngeal tumors, head and neck tumors, or hematological malignancies (*i.e.* acute lymphoblastic leukemia (ALL)) are at risk for developing pituitary hormone deficiencies if the hypothalamus and/or the pituitary have been exposed to radiation (37–39).

Traumatic brain injury

In recent years, several studies have reported a high prevalence of pituitary insufficiency ranging from 15–90% in patients who experienced traumatic brain injury (TBI) (40–51). Large neuropathological series demonstrate pituitary as well as hypothalamic lesions after TBI (52). Infarction is believed to be the cause of posttraumatic hypopituitarism, found at post mortem in 26% to 86% of patients who died after TBI. Possible mechanisms for post-traumatic infarction include compression of the pituitary gland caused by changes in intracranial pressure resulting from cerebral edema, hemorrhage or skull fracture, hypoxia, or direct damage to the gland itself (53;54).

The diagnosis of hypopituitarism, defined as deficient secretion of one or more pituitary hormones secondary to pituitary or hypothalamic disease, is made by documenting subnormal secretion of these pituitary hormones under defined (*i.e.* controlled) circumstances. Since there is a variable pattern of hormone deficiencies among patients with hypopituitarism, each pituitary hormone must be tested separately. For the evaluation of each axis basal serum hormones levels, but also dynamic testing is available.

Growth hormone deficiency

Clinical consequences

Growth hormone deficiency (GHD) in adults is characterized by increased body fat and decreased lean body mass, decreased bone mass and increased fracture rate, impaired cardiac function and reduced muscle strength (55–57). Adult patients with GHD also share a number of characteristics of the metabolic syndrome, including hypertension, abdominal obesity, insulin resistance and dyslipidemia (58). In addition, quality of life is impaired, with reduction in physical and mental energy, increased anxiety, and dissatisfaction with body image and poor memory (2;57;59;60). Replacement therapy with growth hormone (rhGH) was associated with apparent benefits, particularly in terms of body composition, bone mass, muscle strength, cardiac function and quality of life (61).

Diagnosis

Because of the pulsatile nature of GH secretion, basal serum GH levels are not useful to assess the GH-IGF-I axis, although basal serum IGF-I levels below the reference ranges are indicative for GHD in the presence of two or more other insufficiencies (62;63). Normal IGF-I concentrations, however, do not exclude the diagnosis of GHD, as IGF-I levels are within the normal reference range in about one third of patients with GHD, especially in elderly subjects (64–66). Therefore, the use of dynamic testing is mandatory for the evaluation of GH secretory reserve.

Different stimulation tests are available (*i.e.* insulin tolerance test (ITT), and stimulation tests with glucagon, GHRH, GHRH-arginine, or GHRH-GHRP6). However the preferred test for evaluation of this axis still remains the insulin tolerance test (63;67). With the administration of insulin a hypoglycemia is induced which is a very strong physiological stimulator of the stress response. Hypoglycemia activates the hypothalamus to secrete GHRH resulting in stimulation of GH by the somatotropic cells of the pituitary gland. A peak GH response below 3 μg/L indicates a severe GHD (63;67). During ITT simultaneous assessment of the hypothalamus-pituitary-adrenal (HPA) axis is possible. Important contra-indications to perform the ITT are coronary insufficiency and/or epilepsy. To assess the GH axis in these patients, alternative provocative tests for GH secretion must be used with adapted appropriate cut-offs. The combined administration of arginine and GHRH is the most frequently used alternative GH stimulation test (66;68;69). GHRH and arginine both have a stimulatory effect on the pituitary gland (70;71). When given simultaneously they enhance their effect resulting in a secretion of GH. A bolus dose of GHRH (1 μg/kg body weight) is given intravenously at baseline, immediately followed by an intravenous infusion of arginine (0.5 gr/kg body weight (to a maximum of 30 gr)) for 30 minutes. Measurements of GH are done 30, 45, 60 and 90 minutes after infusion. Recently, cut-off values adjusted for both body mass index (BMI) and age have been published (72).

Pitfalls

Several factors play a role when testing the GH secretion reserve, such as age, gender, BMI, other hormones and insulin sensitivity. Obese subjects have a blunted GH response to any provocative stimulus (8;73;74). There is an estrogen-related difference in GH axis activity: GH secreted per burst

greater and 24-hour GH release pattern is less orderly in women than men (75). Finally, GH secretion decreases with increasing age. Therefore, these factors should be considered when defining the diagnostic cut-off points in the assessment of GHD (72;76).

Corticotropin deficiency

Clinical consequences

ACTH deficiency leads to adrenocortical insufficiency, characterized by decreased secretion of cortisol. Normal corticotroph function is mandatory for adequate increase of cortisol concentrations in case of stress. However, to maintain sufficient cortisol concentrations, normal basal secretion of ACTH is necessary.

Hypocortisolism can be secondary to either adrenal gland destruction (primary adrenal insufficiency, mostly auto-immune adrenalitis or tuberculous adrenalitis) or to ACTH deficiency (secondary or central adrenal insufficiency) (77).

Diagnosis

Similar to the secretion of GH, the secretion of ACTH is pulsatile with circadian variation resulting in a circadian rhythm of cortisol secretion. Therefore, it is necessary to evaluate basal serum cortisol secretion in the early morning, during fasting. When cortisol concentrations are lower than, or exceed, a certain threshold (< 100 nmol/L or > 500 nmol/L) the likelihood of the presence or absence of adrenal insufficiency is very high, or negligible, respectively. In these cases stimulatory tests are not necessary (78). In all other condition, a dynamic test is mandatory.

The initial and most convenient test to evaluate the function of the HPA axis is the plasma cortisol response to synthetic ACTH (Synacthen test) (79;80). The test is performed by administering a bolus of 1 or 250 μg of cosyntropin intramuscularly or intravenously with measurements of serum cortisol 30 and 60 minutes thereafter. A serum cortisol concentration of ≥ 500–550 nmol/L is considered a normal response. However, this test does not discriminate between the different causes of adrenal insufficiency, and a normal test response does not exclude mild secondary forms of adrenal insufficiency (81–84).

Other tests, that directly evaluate pituitary reserve are also available (insulin induced hypoglycemia, metyrapone administration, or CRH stimulation). Also in the assessment of the HPA axis (similar to the GH-IGF-I axis) the ITT still remains the golden standard (85;86). Insulin induced hypoglycemia results in stress which actives the entire HPA axis providing proof for adequate hypothalamic (CRH) and pituitary (ACTH) function. In healthy subjects serum cortisol levels will increase above 550 nmol/L if adequate hypoglycemia is achieved (glucose 2.2 mmol/L or lower). Stimulation with metyrapone is an alternative test to assess the HPA axis. The adrenal enzyme 11-ß-hydroxylase (CYP11B1) that catalyzes the conversion of 11-deoxycortisol to cortisol, is inhibited by metyrapone, resulting in a reduction of cortisol secretion. Administration of metyrapone will thus result in activation of the HPA axis, an increase in ACTH secretion and consequently an increase in adrenal steroidogenesis up to 11-deoxycortisol. An 11-deoxycortisol concentration above 200 nmol/L in the presence of suppressed cortisol levels (below 100 nmol/L) is then indicative for central adrenal insufficiency (87–89). This test can be performed as a prolonged and short overnight version, depending on the number of dosages of metyrapone given. It appears, however, that the ACTH stimulus of a single dose of metyrapone is comparable to that of an insulin tolerance test (89).

Since the 1980's ovine CRH is used for the evaluation of the HPA axis, mainly to discriminate between pituitary or adrenal causes of Cushing's syndrome (90-94). However, in recent years the CRH test is more often used to assess secondary adrenal insufficiency (95;96). Administration of an intravenous bolus of ovine CRH results in pituitary ACTH secretion resulting in cortisol secretion by the adrenal glands. In healthy subjects a 1 μg/kg i.v. CRH bolus results in a peak ACTH response within 15 min and a peak cortisol response within 30–60 min. A peak cortisol of 550 nmol/L or higher is considered to be a sufficient reaction. The CRH test however, is inferior to the ITT and metyrapone test (97).

Pitfalls

The use of exogenous corticosteroids can suppress the HPA axis. Therefore, in case of exogenous glucocorticoid use, a reliable evaluation of the HPA axis can not be performed within 6 weeks after withdrawal of the steroid but might even be disturbed many months thereafter. Contraceptives in females should also be stopped for at least 6 weeks

because of the effects of hormonal agents on cortisol binding globulin (CBG) levels (98;99).

Thyrotropin deficiency

Clinical manifestation

The symptoms and signs associated with thyrotropin (TSH) deficiency are similar to those of primary hypothyroidism but usually are less severe, as there often is some residual thyrotropin secretion. In addition, TSH deficiency is almost always part of complete anterior pituitary hormone deficiency because thyreotroph secretion is the most resistant to insufficiency. Tiredness, cold intolerance, weight gain, constipation, dry skin, and hair loss are common features.

Diagnosis

TSH deficiency is diagnosed by low or normal serum TSH concentrations in the presence of low serum free thyroxine (fT_4) level. Measurement of serum fT_3 is not of additional value but may be low or normal. Thyrotropin-releasing hormone (TRH) can be used to assess TSH secretion. However, the response to TRH varies widely among individuals. Therefore it is not possible to discriminate between a normal and abnormal response in the majority of cases and TRH has not been incorporated into routine clinical practice of the evaluation of TSH deficiency (100).

Gonadotropin deficiency

Clinical manifestations

The clinical features of gonadotropin deficiency are determined by gender and the age of development. The physical examination in men with recent onset hypogonadism will usually be normal. However, in longstanding hypogonadism diminished facial and body hair, gynaecomastia, and small, weak testes can be present. Libido may be reduced and the ability to achieve and maintain an erection may be compromised. Patients can also complain of nonspecific symptoms, such as tiredness, reduced muscle strength, reduced exercise capacity, but also emotional lability and depression. The symptoms in men are nonspecific and therefore

may not become evident for many years, particularly if fertility is not an issue (77).

In women gonadotropin deficiency leads to menstrual disturbances (*i.e.* oligomenorrhea or amenorrhea) and therefore often earlier diagnosed compared to men (2).

Diagnosis

The diagnosis in women is straightforward. In premenopausal women secondary amenorrhea with low levels of estradiol and low or nomal levels of gonadotropins will confirm the diagnosis. Whereas, in post-menopausal women FSH and LH will be (undetectably) low.

Low or normal gonadotropin levels combined with serum testosterone levels below the reference range, corrected for age are sufficient to confirm the diagnosis. Because of the great circadian variation randomly found decreased testosterone levels should be repeated in the early morning (between 8–9:00 AM).

Prolactin deficiency

Clinical manifestations

Mild hyperprolactinaemia (up to 5 times the upper limit of normal) is common in patients with hypopituitarism. A pituitary mass with supra-sellar extension may compress the stalk resulting in decreased dopaminergic inhibition of prolactin secretion.

Raised prolactine levels effects pulsatile secretion of gonadtropins resulting in hypogonadism. Galacthorrhea can also be present. Prolactin deficiency almost invariably results from lactotroph deficiency secondary to hypothalamic damage as a result of irradiation and or surgery.

Diagnosis

The diagnosis of prolactin deficiency is straightforward using commercially available assays with gender adjusted reference ranges for the determination of prolactin concentrations. However, unless it is in the postpartum period, there are no clinical implications.

IV. Outline of this thesis

Pituitary insufficiency in the presence of a pituitary macroadenoma or after pituitary irradiation is frequently reported. In addition, pituitary insufficiency is increasingly reported after traumatic head injuries. The correct evaluation and interpretation, however, of the pituitary axes, and consequently, the potential therapeutical consequences are a matter of controversies. The studies reported in this thesis aim 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.

The evaluation of pituitary function in patients after traumatic brain injury

Traumatic brain injury (TBI) has emerged as an important cause of hypopituitarism. However, considerable variations in the prevalence of hypopituitarism are reported. These variations can partly be explained by the severity of trauma and timing of hormonal evaluation, but may also be dependent on endocrine tests and criteria used for diagnosis of hypopituitarism. Therefore, in **chapter 2**, we performed a systematic review of the literature to critically compare pituitary function tests, and definitions of hypopituitarism in studies that assessed the long-term outcome of TBI on pituitary function.

Because of the great variation in prevalence rates reported and the great variation in endocrine assessments used, we decided to perform a cross-sectional study in the Netherlands of a large cohort of 112 TBI patients evaluated after long-term follow-up. We assessed the prevalence of pituitary insufficiency in our own large cohort of TBI patients using a standardized endocrine evaluation, described in **chapter 3**. In these patients, we also evaluated quality of life (QoL) using different QoL questionnaires.

Dynamic tests of pituitary function in other pituitary diseases

Pituitary adenomas and their treatment (*i.e.* surgery and/or radiotherapy) are also causes for pituitary insufficiency. Pituitary insufficiency is a complication that can be attributed to the tumor itself (compression) but also to the surgical approach and/or subsequent radiotherapeutical intervention. Therefore, accurate assessment of pituitary function is critical for appropriate management of patients with pituitary adenoma after surgery with or without irradiation. For many years, all patients in our hospital underwent a CRH stimulation test for the evaluation of the HPA axis shortly after pituitary surgery. In **chapter 4,** we describe a retrospective study that evaluated the clinical applicability of the CRH test directly after TS in our center.

The ITT, however, is considered the golden standard test for the evaluation of the HPA axis. In **chapter 5,** we describe a study on the long-term prevalence of adrenal insufficiency after transsphenoidal surgery for growth-hormone secreting pituitary adenomas using the ITT and CRH test in the majority of the patients. The reason for this evaluation was a recently published study that reported a remarkably high prevalence of adrenal insufficiency after surgical and/or medical treatment without postoperative radiotherapy in patients treated for acromegaly. Therefore, in our study, we evaluated the prevalence and incidence rate of adrenal insufficiency in 91 consecutive patients during long-term follow-up after successful transsphenoidal surgery for acromegaly.

In addition to patients with pituitary tumors, patients with nonpituitary intracranial and or nasopharyngeal tumors are treated by radiotherapy, in which the pituitary gland is involved in the radiation field. These patients are also at risk for pituitary insufficiency. To assess the prevalence of possible pituitary insufficiencies 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**.

Treatment of GH deficiency

When growth hormone deficiency is diagnosed, the therapeutical consequences should be carefully evaluated, especially in certain conditions like obesity and during senescence where GH secretion overlaps with a GH deficient state. With increasing age, but also increasing BMI, GH secretion decreases. Therefore, the effects of treatment with rhGH in obesity and in the elderly diagnosed with GHD might be different.

Therefore, in **chapter 7,** we performed a structured review, to critically assess the available literature in order to evaluate the available evidence for treatments of elderly patients with GHD.

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Chapter 2

Clinical review: Hypopituitarism following traumatic brain injury – the prevalence is affected by the use of different dynamic tests and different normal values

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Abstract

Objective: Traumatic brain injury (TBI) has emerged as an important cause of hypopituitarism. However, considerable variations in the prevalence of hypopituitarism are reported. These can partly be explained by severity of trauma and timing of hormonal evaluation, but may also be dependent on endocrine tests and criteria used for diagnosis of hypopituitarism.

Methods: Systematic review of studies reporting prevalence of hypopituitarism in adults ≥ 1 year after TBI focusing on used (dynamic) tests and biochemical criteria.

Results: We included data from 14 studies with a total of 931 patients. There was considerable variation in definition of hypopituitarism. Overall, reported prevalences of severe GH deficiency varied between 2 and 39%. Prevalences were 8–20% using the GHRH-arginine test (cut-off < 9 μg/L), 11–39% using the glucagon test (cut-off 1–5 μg/L), 2% using the GHRH test (no cut-off) and 15–18% using the insulin tolerance test (ITT) (cut-off < 3 μg/L).

Overall, the reported prevalence of secondary adrenal insufficiency had a broad range from 0 to 60%. This prevalence was 0–60% with basal cortisol (cut-off < 220 or < 440 nmol/L), 7–19% using the ACTH test and 5% with the ITT as first test (cut-off < 500 or < 550 nmol/L). Secondary hypothyroidism was present in 0–19% (free T_4) or 5–15% (TRH stimulation). Secondary hypogonadism was present in 0–29%.

Conclusion: The reported variations in the prevalence rates of hypopituitarism after TBI are 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.

Introduction

In recent years, an increasing number of studies have reported the presence of pituitary insufficiency in patients who experienced traumatic brain injury (TBI) (1–14). The prevalence of pituitary insufficiency after TBI appeared to be unexpectedly high (15;16). Remarkably, the prevalence rates varied considerably among the different studies, ranging from 15 to even 90% of the patients.

Several factors influence the prevalence of hypopituitarism after TBI. First, the time interval between TBI and the assessment of pituitary function, since hormone alterations mimicking pituitary insufficiency are prevalent in the early post-traumatic period. Second, the type and severity of the brain injury affects the prevalence of hypopituitarism, because persistent pituitary insufficiency is only frequent after severe TBI (7;15). Third, endocrine tests, assays, and criteria for the diagnosis of hypopituitarism differ between the studies. Although many reviews have addressed TBI-related hypopituitarism, a detailed comparison of these methodological issues between the different studies has not been performed for each pituitary axis.

We hypothesized that these methodological differences may have contributed, at least in part, to the discrepancies in prevalence rates of hypopituitarism after TBI, reported by the different studies. Therefore, the aim of this study 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.

Patients and methods

Search strategy

We performed a search in PubMed, EMBASE, Web of Science, and the Cochrane database, for all published studies on the association between TBI and hypopituitarism. The following search strategy was used: *(Traumatic Brain Injury OR Traumatic brain injuries) AND (traumatic OR trauma) AND (Hypopituitarism OR Hypopituitar* OR Hypothalamus Hypophysis System OR "Hypothalamopituitary dysfunction" OR "pituitary dysfunction" OR Hypothalamo-Hypophyseal System OR Pituitary Gland OR Hypophysis).*

In addition, the references of relevant articles were checked for additional articles. The search was performed on 23 March 2009. Only original articles were included. We used the following exclusion criteria: pediatric or adolescent population, publications concerning pituitary testing < 12 months after injury (a median of 12 months was accepted), and articles that evaluated pituitary insufficiency after subarachnoidal bleeding (SAB).

Data review

The following data were extracted from each study: 1) age and gender, 2) the endocrine tests used for assessment of each pituitary axis, 3) definitions used for pituitary insufficiency for each pituitary axis, 4) hormone assays, 5) reference values provided in the manuscript, and 6) use of control populations. Tables were constructed per pituitary axis. These tables are added as supplemental data files. The growth hormone (GH)-IGF-I axis (Table 2), the pituitary-adrenal axis (Table 3), the pituitary-thyroidal axis (Table 4), the pituitary-gonadal axis (Table 5), and prolactin (Table 6).

Results

We identified 278 articles, of which 218 were excluded on the basis of title and abstract. Of the remaining 60 articles, 46 were reviews. Finally, 14 original studies were included with a total of 931 patients. Details of these studies are summarized in Table 1. The number of patients evaluated by the different studies varied between 22 and 105.

Table 1. Studies on TBI and pituitary deficiency

Study	Year of publication	No. of patients	Time of testing post TBI [months (median)]	Trauma severity (GCS)	BMI (kg/m²)	Any pituitary deficiency (%)
Kelly *et al.*(6)	2000	22	3–276 (median 26)	3–15	25.1±6.5	37
Lieberman *et al.*(9)	2001	70	1–276 (median 13)	3–15 84% GCS ≤ 8	NR	69
Bondanelli *et al.*(3)	2004	50	12–64	3–15 54% GCS ≤ 8	24.6±0.4	54
Agha *et al.*(1)	2004	102	6–36 (median 17)	3–13 56% GCS ≤ 8	NR	28
Popovic *et al.*(10)	2004	67	12–264	3–13	24.8±0.5	34
Aimaretti *et al.*(2)	2005	70	12	3–15 21% GCS ≤ 8	23.8±0.4	23
Leal-Cerro *et al.*(8)	2005	99	>12	≤ 8	25.2±3.0 (n=44)	25
Schneider *et al.*(11)	2006	70	12	3–15	23.8±3.2	36
Tanriverdi *et al.*(12)	2006	52	12	3–15 25% GCS ≤ 8	NR	51
Herrmann *et al.*(5)	2006	76	5–47	≤ 8	25.8±4.2	24
Bushnik *et al.*(4)	2007	64	> 12 months	NR	NR	90
Klose *et al.*(7)	2007	104	10–27 (median 13)	3–15 38% GCS ≤ 8	25* (17–39)	15
Tanriverdi *et al.*(14)	2008	30	36	3–15 16.7% GCS ≤ 8	NR	30
Wachter *et al.*(13)	2009	55	NR	3–15 17% GCS ≤ 8	NR	25
Total No. of patients:		931				

BMI, body mass index reported as the mean ± SEM ; GCS, Glasgow Coma Scale sore; TBI, traumatic brain injury; NR, not reported. * reported as median (range)

The GH-IGF-I axis

The prevalence of GH deficiency (GHD) ranged between 2 and 66% (severe GHD 39%; Figures 1 and 2 and Suppl Table 2). The presence of GHD was associated with higher body mass index (BMI) values in some of the studies (Figure 1). In addition to basal serum GH and IGF-I values, all studies used a dynamic test to assess GH secretory reserve. However, different dynamic tests were used.

Three studies (196/931=21% of all patients) used the combined GHRH-arginine test as the first screening. The criterion for severe GHD was a peak GH level < 9.0 μg/L in all three, which was not adjusted for BMI. Prevalence rates of severe GHD varied between 8 and 20% (weighted mean 12%) (2;3;5). Schneider *et al.* (11) also used the GHRH-arginine test, but only in a subset of the patients (those with abnormal serum cortisol levels, n=32); the prevalence of GHD in this study was 10%.

Two studies (112/931=12% of all patients) used an insulin tolerance test (ITT) as the primary screening test (6;7). The criterion for severe GHD was a peak GH response < 3 μg/L in both, and the prevalence of GHD was comparable (18 and 15% respectively; weighted mean 16%).

Of the eight remaining studies, three used a stimulation test with glucagon (n=209) (1;4;9) with prevalence rates for severe GHD between 11 and 39% (weighted mean 20%). The cut-off values differed considerably and varied between 1 and 5 μg/L between these studies. Just one study used a stimulation test with GHRH only (number of patients not recorded) reporting a GHD prevalence of 2% (13). Two studies (n=119) used the combined GHRH-GHRP6 test with a prevalence of 15 and 33% respectively (weighted mean 21%) (10;12). The cut-off values were similar (GH < 10 μg/L) within these studies, and were derived from another report (17).

Finally, two studies used a combination of these tests (8;14). For instance, Agha *et al.* (1) used a glucagon stimulation test for the initial screening in 102 subjects, and in case of incomplete GH response, they used an ITT (n=14) or combined GHRH plus arginine test (n=4) to confirm GHD.

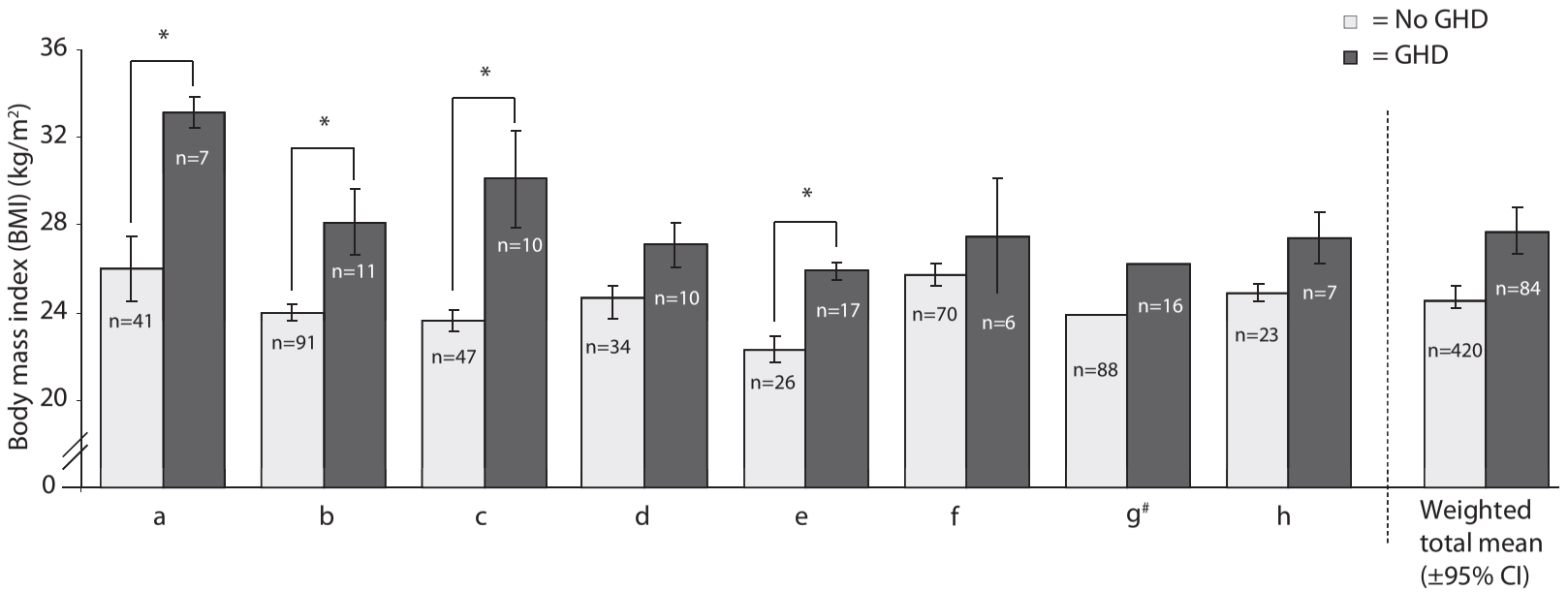

Figure 1. Body mass index in patients diagnosed with versus those without GH deficiency (data available only in 8 out of the 16 studies). a, Lieberman *et al.* 9); b, Agha *et al.*(1); c, Popovic *et al.* (10); d, Leal-Cerro *et al.* (8); e, Tanriverdi *et al.*(12); f, Herrmann *et al.*(5); g, Klose *et al.*(7); h, Tanriverdi *et al.*(14); i, weighted total mean (mean±95% CI: no GHD 24.5 (24.2–24.9) versus GHD 27.7 (26.7–28.8) kg/m^2). GHD, GH deficiency; BMI, body mass index; *P<0.05. #Data reported as median with range; not included in the total weighted mean.

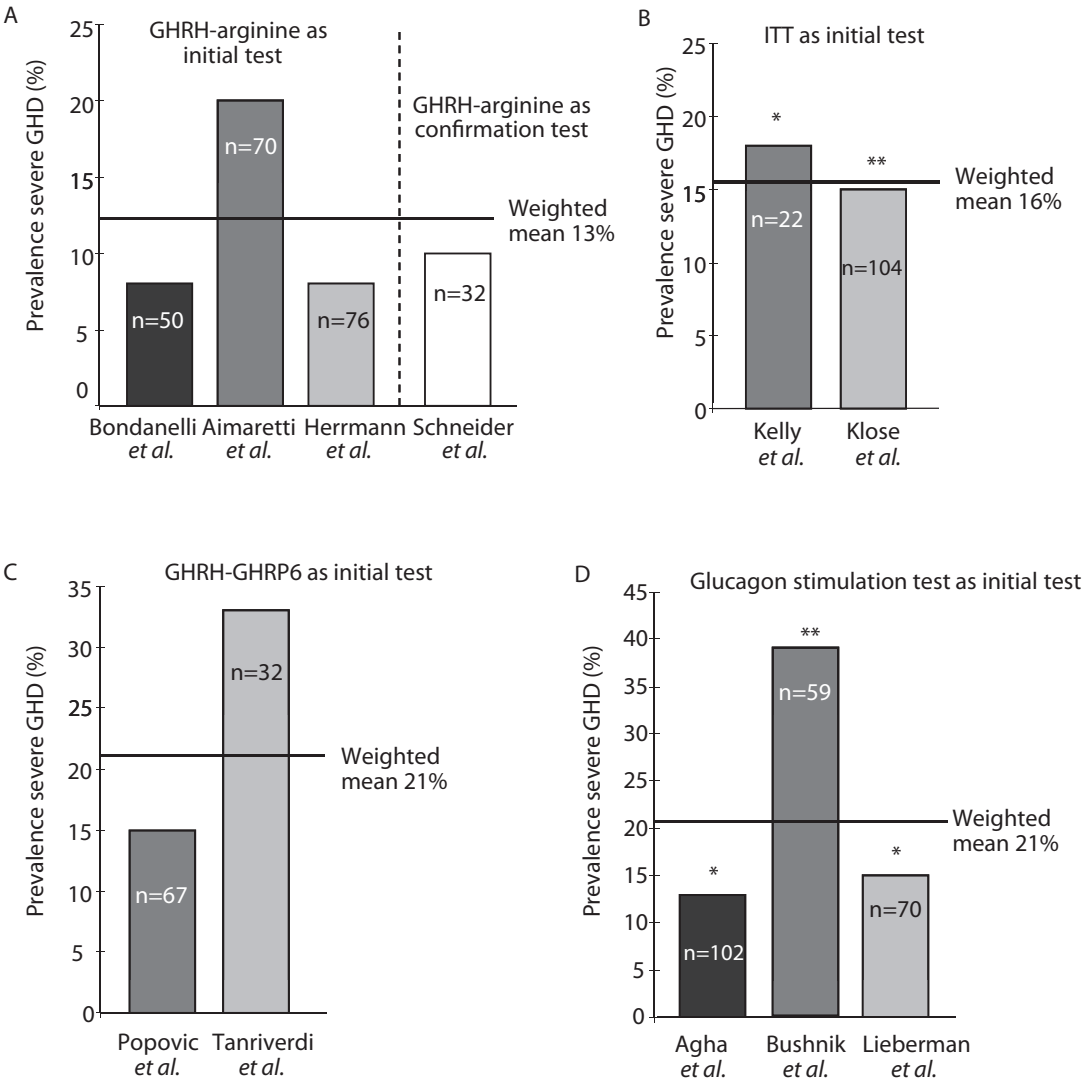

Figure 2. Absolute and weighted mean prevalence rates of severe GH deficiency (GHD) according to the stimulation tests used per study. The number of patients tested is depicted in each bar. *Panel A:* the combined GHRH-arginine test; definition severe GHD: peak GH < 9 µg/L for all four studies. *Panel B:* the insulin tolerance test (ITT); *definition severe GHD: GH < 95% CL according to AUC; **definition severe GHD: peak GH < 3 µg/L. *Panel C:* the combined GHRH-GHRP6 test; definition severe GHD: peak GH < 10 µg/L for both studies. *Panel D:* the glucagon stimulation test; definition severe GHD: *peak GH < 3 µg/L; **peak GH < 5 µg/L. *Panel E:* combined stimulation tests as initial screening followed by confirmation test; ΔGHRH-GHRP6 test as initial test; ITT and glucagon stimulation test as confirmation tests; ΔΔGHRH-GHRP6 test as initial test; glucagon stimulation test as confirmation test.

The Pituitary-Adrenal axis

The prevalence of secondary adrenal insufficiency deficiency ranged from 0 to 60% between the studies (Figure 3, Suppl Table 3).

Four studies (251/931=27% of all patients) only measured basal morning fasting serum cortisol and/or ACTH levels (2–4;10), resulting in prevalence rates between 0 and 60% (weighted mean 15%). The criteria for pituitary-adrenal insufficiency differed between three studies (cortisol < 220–440 nmol/L), and were not reported in the fourth study (10). The study reporting the highest prevalence of 60% used a cut-off value of 440 nmol/L (4).

Four studies (145/931=12% of all patients) used an ACTH stimulation test (Synacthen; either with 1 or 250 μg). However, only one study performed this test in all patients and the prevalence of ACTH deficiency was 7% (9). In the other three studies, only a subset of the patients (those with subnormal basal cortisol levels) underwent stimulation with ACTH. The prevalence in these studies varied between 7 and 19% (weighted mean 10%) (11;12;14).

One study (55/931=6% of all patients) used nonstimulated cortisol values between 1600 and 2000 h (reference values 63–339 nmol/L), which was followed by a corticotrope releasing hormone (CRH) test only in those with values below this reference range, or in those who responded confirmatory to a specific questionnaire (13).

In the remaining five studies (403/931=43% of all patients), the ITT was used in 169 patients as a primary test (n=112) resulting in a prevalence of 5% in both studies (6;7), or as a confirmation test in a subset of the patients. Two studies measured basal serum cortisol levels and used ITT as a confirmation test (prevalence of 3 and 11% respectively) (5;8). One study assessed primarily with a glucagon stimulation test (n=102), and used the ITT and ACTH tests to confirm ACTH deficiency (prevalence 13%) (1). The criteria for a normal cortisol response to hypoglycemia were a peak cortisol level > 550 nmol/L in one (8), and > 500 nmol/L in three other studies (1;5;7). The fifth study used a control group of 18 healthy subjects to define normal cortisol responses to ITT (cortisol response < 95% confidence limit according to the obtained area under the curve) (6). The CRH test was used in only one study and did not report the number of patients (13).

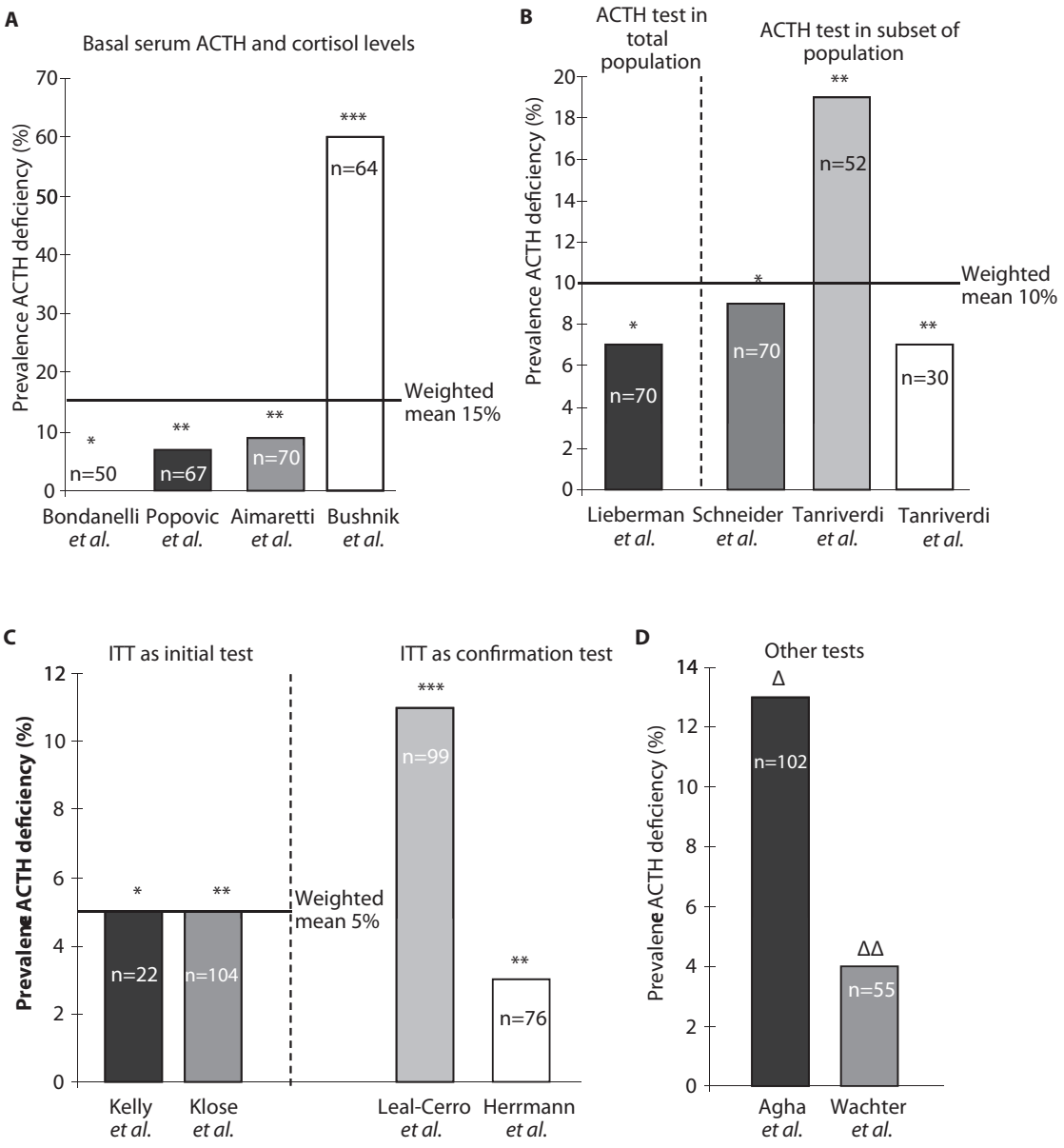

Figure 3. Absolute and weighted mean prevalence rates of corticotropin (HPA axis) deficiency according to the stimulation test used per study. The number of patients tested is depicted in each bar. *Panel A:* basal cortisol concentrations only using different cut-off levels; *cut-off level: NR; **cut-off level: cortisol < 220 nmol/L; ***cut-off level: cortisol < 440 nmol/L. *Panel B:* the ACTH stimulation test *using 250 µg ACTH and peak cortisol < 500 nmol/L; **using 1 µg ACTH and peak cortisol < 550 mol/L. *Panel C:* the insulin tolerance test (ITT); *peak cortisol < 95% CL according to AUC; **peak cortisol < 500 nmol/L; ***peak cortisol < 550 nmol/L. *Panel D:* other stimulation tests: Δthe glucagon stimulation test; ΔΔCRH test.NR, not reported.

The Hypothalamus-Pituitary-Thyroid axis

The prevalence of hypothalamus-pituitary-thyroid axis deficiency ranged from 0 to 19% between the studies (Suppl Table 4).

The criteria for TSH deficiency were different. Nine studies used basal free thyroxine (fT_4) and TSH levels only. Within these studies, the cut-off value for decreased fT_4 varied between 8 and 12 pmol/L (2;5;7;11;14;18;19). In two studies, reference values were not reported (4;10), one of which (Bushnik *et al.*) reported the highest prevalence of secondary hypothyroidism.

The thyroid-releasing hormone (TRH) stimulation test was used in five studies, using i.v. doses of 200 (13) and 500 µg (5;6;8;9). The criterion for a normal response differed considerably: a TSH peak response > 7 mIU/L, a TSH peak between 5 and 30 mIU/L, or were not reported (12;13).

The prevalence rates between the studies that only measured basal fT_4 levels varied between 0 and 19% (weighted mean 5%) (1–5;7;10;11;14), and between 5 and 15% (weighted mean 8%) in those that also used TRH (6;8;9;12;13).

The Hypothalamus-Pituitary-Gonadal axis

The hypothalamus-pituitary-gonadal axis deficiency ranged from 0 to 29% (weighted mean 13%) between the studies (Table 5). Basal LH and FSH were measured in all but one study (4). Basal estradiol (E_2 in women) was measured in 9 studies, and the menstrual history was recorded in 10 out of 14 studies. Testosterone (in men) was measured in all studies. In four studies, a GnRH stimulation test was performed in a subset of the patients (6;8;9;13). The criterion for a normal test response differed between the studies (Suppl Table 5). The definition of secondary hypogonadism was mainly based on basal testosterone (in men) and E_2 concentrations (in women) below the reference ranges, in the presence of decreased or normal LH and FSH levels. A subset of the studies also incorporated the GnRH test result (see above) and menstrual cycle abnormalities in premenopausal females.

Prolactin

The prevalence of abnormal serum PRL concentrations ranged from 0 to 16% (Suppl Table 6). Abnormal PRL secretion was defined as hyperprolactinemia (8/14 studies) (1;2;5;7;9;11;12;14), hypoprolactinemia

(one study) (6), or both (3). In accordance, prevalence rates were between 3 and 12% using the definition of hyperprolactinemia, 0% using the definition of hypoprolactinemia, and 16% using the combination of both. Out of the 14 studies, 10 measured basal serum PRL concentrations only (1–3;5;7;9–12;14). Three studies also used a TRH test (doses 100 and 500 μg respectively) (6;8;13). Prevalence rates were not reported in two of these (8;13) and were 0% in the third (6).

Discussion

This review demonstrates that the endocrine evaluations and definitions of hypopituitarism differ considerably among the studies that have assessed TBI-related hypopituitarism. From the existing literature, the notion emerges that most of the tests that are currently used to establish the diagnosis of hypopituitarism in general, and GHD in specific, are not validated sufficiently regarding cut-off values, reproducibility, and dependence on confounding factors in TBI patients.

In general, there are hardly any data on reproducibility of tests or dependence on confounding factors in TBI patients. One factor that comes forward in the current review is the potential effect of increased BMI, which in general is associated with decreased GH responses to GH stimulation tests. Therefore, increased BMI may result in an inadvertently higher incidence rate of GHD, if the cut-off values for normal GH responses to GH stimulation tests are not adapted according to BMI. All these methodological issues limit the applicability of the individual studies, *i.e.* the decision whether the study results are valid for patients to whom the results are generalizable but who are subjected to a different endocrine diagnostic assessment than the original study population. Moreover, these methodological limitations prohibit simple generalizations of the results from the perspective of a meta-analysis or a review.

The question arises whether post-traumatic hypopituitarism, especially GHD, has been overdiagnosed on the basis of the older cross-sectional studies. Consensus guidelines for the evaluation of adult GHD state that different dynamic tests can be used to diagnose GHD, including the ITT, the glucagon stimulation test, the combined GHRH-arginine test, and the combined GHRH-GHRP6 test (20). The present assessment, however, documents a higher prevalence of GHD for the glucagon stimulation test and the combined GHRH-GHRP6 test, compared to the results of the combined GHRH-arginine test and the ITT. With the exception of the ITT (which was used in only 12%

of the patients (6;7)), the outcome of each test varied greatly (Figure 2) using different (glucagon stimulation test) or similar cut-off levels (other test). In addition, the studies that used two dynamic tests to assess GH reserve revealed a lower prevalence of GHD than the studies with only one test. Moreover, the results of GH stimulation tests are confounded by BMI, with higher BMI being associated with decreased GH responses. Although BMI-adjusted reference values have been reported (21), none of the studies on TBI-associated GHD reports adjusted their cut-off values for BMI. Moreover, the data indicate that BMI tends to be higher in the TBI patients with GHD (Figure 1). Finally, an important aspect is that most patients had only GHD or one additional pituitary hormone deficiency. Therefore, one test may not be sufficiently reliable and the use of two tests would increase the confidence in the diagnosis, although only if the two tests yield concordant results. However, the application of two tests may introduce an even greater uncertainty in case of discordant results. This discrepancy has been documented for instance in GHD in irradiated patients, in whom the attenuation in GH responses to the ITT was greater compared with the combined GHRH-arginine test (22). These factors impose major problems for an accurate assessment of GHD in these patients. Therefore, these methodological issues have contributed to the suspicion that GHD is probably over diagnosed in the older cross-sectional studies.

We observed similar variations in test results of the pituitary-adrenal axis (Figure 3). The use of different tests with different cut-off values resulted in prevalence rates that varied between 5 and 19%. ACTH deficiency can be diagnosed by measuring basal early morning cortisol levels: values below 100 nmol/L are indicative of ACTH deficiency, whereas cortisol values above 500 nmol/L essentially exclude ACTH deficiency. The ACTH stimulation test is reliable in diagnosing clinically significant adrenal insufficiency in patients who are at risk (23–25). ACTH stimulation tests, however, are not fully reliable in excluding the presence of mild secondary adrenal insufficiency (26). The ITT still remains the golden standard, and has the advantage that ACTH/cortisol and GH secretory reserve can be assessed simultaneously. If an ITT is contraindicated, a CRH test can be alternatively used (27). The effect of the initial choice for a specific stimulation test on the variation in outcome of adrenal insufficiency and GHD based on the available data after TBI is illustrated in Figure 4.

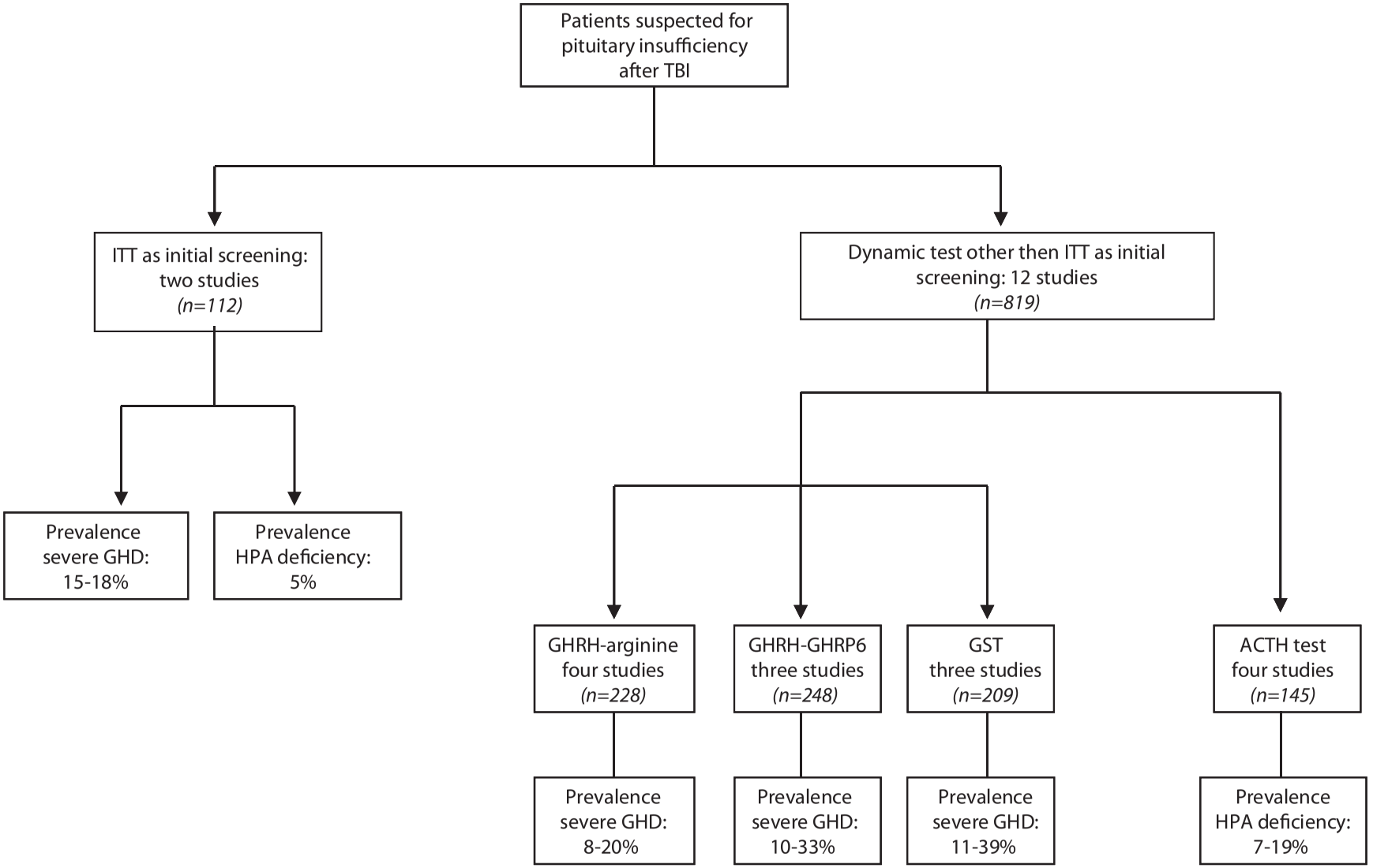

Figure 4. Example illustrating the effect of initial test choice on the variation in outcome of prevalence rates of severe GHD and HPA axis insufficiency.

The diagnosis of secondary hypothyroidism is usually made based on fT_4 values. However, basal fT_4 levels show a relatively small intra-individual variability, although inter-individual variability is large (28). As a consequence, a diagnosis of possible secondary hypothyroidism may not be straightforward, since fT_4 levels within the normal reference range can reflect hypothyroidism in one patient but euthyroidism in another patient. Basal TSH levels are also of limited help for the diagnosis of secondary hypothyrodism, since normal or even increased levels of TSH can be found (29). In addition, a TRH test is of limited value because patients with central hypothyroidism may show different patterns of TSH responses to TRH, with absent or exaggerated responses, which considerably overlap with those found in healthy volunteers. Moreover, the magnitude of the TSH peak is proportional to the injected TRH dose, is higher in women, and tends to decline with age (30). In accordance, the prevalence rates were not affected by the use of TRH stimulation. In analogy, the interpretation of the GnRH test is complex, and individual responses vary greatly in both adults and children (31). In men, it is sufficient to measure non-stimulated LH, FSH, and testosterone concentrations. In premenopausal women, the evaluation of the menstrual cycle is a prerequisite, whereas in postmenopausal women, the absence of increased LH and FSH levels almost invariably indicates hypogonadotropic hypogonadism.

Analytical factors will most likely also have affected the different outcomes of the studies. For instance, the GH and cortisol assays varied between studies, and it is known that the between-laboratory performance of the GH assay is not very good. Moreover, most were not validated sufficiently regarding normal cut-off values, reproducibility, and dependence on confounding factors even in a 'normal' population. None of these tests have been validated in TBI patients at all.

The time point of evaluation may also influence outcome; therefore, we focused only on studies in the chronic phase after TBI, *i.e.* one year after the trauma. Studies that analyzed patients with a median duration of 12 months after TBI, however, were also included. Thus, part of these patients was assessed within 12 months after TBI. In general, the transient effects of TBI mimicking pituitary insufficiency are almost exclusively reported only within the first six months after TBI (15). Therefore, it is unlikely that the pituitary results of the studies with a median duration of follow-up of 12 months of TBI are caused by the transient effects of

TBI. This is supported by similar results of additional analyses of the remaining studies, which included only patients with a follow-up of more than 12 months after TBI. Lastly, the underlying mechanisms of TBI-related hypopituitarism have not been resolved. It is unclear to that extent hypothalamic versus pituitary damage is present in TBI patients with hypopituitarism and what impact these processes may have on endocrine tests.

Recently, many clinical reviews have summarized the studies on pituitary insufficiency after TBI (15;16). These studies concluded that hypopituitarism is a common complication of TBI and might contribute to morbidity and poor recovery after brain injury (16). However, these reviews did not take into account the variability in diagnostic strategies and definitions of pituitary insufficiency. These discrepancies, in addition to differences in inclusion and exclusion criteria, limit the possibility to compare the results of studies on TBI. We agree with Klose and Feldt-Rasmussen that 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 (15).

In conclusion, the reported prevalence rates of pituitary insufficiency after TBI vary considerably, which is associated with major differences in endocrine and analytical methods of assessment and definitions used for hypopituitarism. This does not only apply to the case of TBI-related hypopituitarism, but most likely also to hypopituitarism caused by pituitary diseases. The same caution with respect to the evaluation of pituitary function should be considered in pituitary diseases, because the diagnosis of definitive hypopituitarism remains a challenge in clinical endocrinology. In pituitary pathology, definitive data on robust accuracy of basal or dynamic hormonal tests are incomplete.

Supplemental data

Table 2. GH-IGF-I Axis

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Kelly *et al.* (6)	22	+	+	+ (n=22)	–	–	GH < 95% CL according to AUC[a]	16–24 yr: 182–780 µg/L 25–39 yr: 114–492 µg/L 40–54 yr: 90–360 µg/L	IFA/RIA*	18[b]
Lieberman *et al.*(9)	70	+	+	–	–	+[c] (GST; n=48)	Peak GH < 3 µg/L	NR	IRMA/RIA*	15
Bondanelli *et al.* (3)	50	+	+	–	+ (n=50)	–	Peak GH < 16.5 µg/L Severe GHD = GH < 9 µg/L Partial GHD = GH 9–16.5 µg/L	20–30 yr : 135–485 µg/L 31–40 yr: 120–397 µg/L 41–50 yr: 113–306 µg/L 51–60 yr: 100–250µg/L >60 yr: 92–229 µg/L	IRMA/RIA	Partial:28 Severe:8
Agha *et al.* (1)	102[d]	+	+	+ (n=14)	+ (n=4)	+[e] (GST; n=102)	GST: peak GH < 5 µg/L ITT: peak GH < 5 µg/L GHRH-arg: peak GH < 9 µg/L	IGF-I SDS: ln(IGF-I) – [5.9 –(0.0146xage in yrs)]/0.272	IRMA/ IRMA	11

Table 2. Continued

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Popovic *et al.*(10)	67	+	+	–	–	+ (GHRH-GHRP6; n=67)	Severe GHD = peak GH < 10.0 µg/L GHI = peak GH < 10.0–20.0 µg/L	Normal levels matched for age and sex 11–35 nmol/L	IRMA/ RIA	Partial: 30 Severe: 15
Aimaretti *et al.*(2)	70	+	+	–	+ (n=70)	–	Peak GH < 16.5 µg/L Severe GHD = peak GH < 9.0 µg/L	25th centile age-related normal limits	IRMA/RIA	Partial: 39 Severe: 20
Leal-Cerro *et al.*(8)	99	+	+	+ (n=35)	+	+[f] (GHRH-GHRP6; GST n=44)	GHRH-GHRP6: peak GH ≤ 10 µg/L GST and ITT: GH 3 µg/L	IGF-I < 200 µg/L (±2SDS)	IRMA/ IRMA*	10
Schneider *et al.*(11)	70	+	+	–	+[g] (n=32)	–	GH < 9.0 µg/L	Age-dependent SDS[h]	CLA/CLA	10
Tanriverdi *et al.*(12)	52	+	+	–	–	+ (GHRH-GHRP6; n=52)	GH < 10 µg/L	IGF-I < 84 µg/L	IRMA/ IRMA*	33

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays	Outcome
							GH	*IGF-I*	GH / IGF-I	(%)
Herrmann *et al.*(5)	76	+	+	+ (n=7)	+ (n=76)	–	GHRH-arg: GH < 9 µg/L ITT: GH peak <3 µg/L	16–24 yr: 182–780 µg/L 25–39yr: 114–492 µg/L 40–54 yr: 90–360 µg/L ≥ 55 yr: 71–290 µg/L	CLA/IRMA	8
Bushnik *et al.*(4)	64	+	+	–	–	+ (GST; n=59)[i]	Severe GHD = peak GH < 3 µg/L Moderate: peak GH 3 –9.9 µg/L	IGF-I age-corrected normal levels	NR	Partial: 66 Severe: 39
Klose *et al.* (7)	104[j]	+	+	+ (n=90)	+ (n=14)	–	Severe GHD = ITT: peak GH< 3 µg/L GHRH-arg: GH< 9 µg/L Partial GHD: = ITT: peak GH 5 µg/L ≤ GH ≥ 3 µg/L GHRH-arg: peak 16.5 µg/L ≤ GH ≥ 9 µg/L	IGF-I SDS[k]	FIA/RIA	15
Tanriverdi *et al.*(14)	30	+	+	–	–	+ (GRHR-GHRP6 n=30; GST n=7)[l]	GRHR-GHRP6: severe GHD = GH < 10 µg/L GST: GH < 1.18 µg/L	18–30 yr: 197–476 µg/L 31–40 yr: 100–494 µg/L 41–70 yr: 101–303 µg/L	IRMA/ IRMA*	23

Table 2. Continued

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Wachter *et al.*(13)	55	+	+	–	–	+ (GHRH; n=NR)[m]	NR	Age adjusted: 116–270 µg/L	NR	2

ACS, Automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; CLA, chemiluminometric assay; FIA, fluoroimmunoassay; GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GRHR, growth hormone releasing hormone; GHRH-GHRP6 test, growth hormone releasing hormone plus growth hormone releasing peptide 6; GST, glucagon stimulation test; IGF-I, insulin-like growth factor I; IRMA, immunoradiometric assay; ITT, insulin tolerance test; NR, not reported; RIA, radio immunometric assay

[a] Normal values defined by a group of healthy subjects (n=18)

[b] ¾ patients with GHD had been tested < 12 months post TBI (7,5,5 months)

[c] GST in n=48; n=20 underwent L-dopa test

[d] Cut-off values defined by 31 healthy control subjects

[e] All patients underwent GST; patients with abnormal results underwent ITT (n=14) or GHRH+arg test (n=4)

[f] Patients with IGF-I in lower range were tested with GHRH-GHRP6 (n=44,glucagon stimulation test (n=44) and ITT (n=35)

[g] 38 healthy controls underwent GHRH-arg test to test appropriatness of cut-off values

[h] Calculated according to Brabant *et al.*2003(31)

[i] GST: 0.03 mg kg-1 max 1 mg intramuscular

[j] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[k] Calculated by Juul *et al.* 1994(32)

[l] Patients with uncertain levels of GH after GHRH-GRHP6 (GH 11–19 µg/L) test underwent GST (n=7)

[m] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests. GHRH: 100 µg

* After acid-ethanol extraction

Table 3. Hypothalamic-Pituitary Adrenal Axis

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH-deficiency	Assay cortisol/ ACTH	Outcome (%)
Kelly *et al.* (6)	22	+	+	–	–	+ (n=22)	–	Cortisol < 95% CI according to AUC[a]	RIA/IRMA	5
Lieberman *et al.* (9)	70	+	–	–	+ (n=70)[b]	–	–	Peak cortisol < 500 nmol/L	MSA/-	7
Bondanelli *et al.* (3)	50	+	+	–	–	–	–	Cortisol and ACTH below reported reference range (cortisol: 220 – 700 nmol/L ACTH: 1.5–11.5 pmol/L)	RIA/IRMA	0
Agha *et al.* (1)	102[c]	+	+	–	+ (n=8)[d]	+ (n=15)	+ (GST; n=102)[e]	Failing 2 tests: GST: peak cortisol < 450 nmol/L ITT: peak cortisol < 500 nmol/L SST: peak cortisol <500 nmol/L	FIA/IRMA	13
Popovic *et al.*(10)	67	+	–	–	–	–	–	NR	RIA/-	7
Aimaretti *et al.*(2)	70	+	–	–	–	–	–	Cortisol < 220 nmol/L 24h urinary free cortisol < 30 µg/24 h	RIA/-	9

Table 3. Continued

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH–deficiency	Assay cortisol/ ACTH	Outcome (%)
Leal-Cerro *et al.*(8)	99	+	+	–	–	+[f] (n=NR)	–	Basal cortisol < 200 nmol/L Peak cortisol < 550 nmol/L Peak ACTH < 6.6 pmol/L	FIA / IRMA	11
Schneider *et al.*(11)	70	+	–	–	+ (n=33)[g]	–	–	Cortisol < 500 nmol/L	ECLIA/-	9
Tanriverdi *et al.*(12)	52	+	+	–	+ (n=12)[h]	–	–	Basal cortisol < 193 nmol/L ACTH test: Cortisol < 552 nmol/L	RIA/IRMA	19
Herrmann *et al.*(5)	76	+	+	–	–	+ (n=7)[i]	–	Cortisol and ACTH below reported reference range (cortisol 180–640 nmol/L; ACTH 3.74– 11.44 pmol/L) ITT: Peak cortisol < 500 nmol/L	IA/CL	3
Bushnik *et al.*(4)	64	+	–	–	–	–	–	Fasting serum cortisol < 440 nmol/L	NR	60
Klose *et al.* (7)	104[j]	+	+	–	+ (n=14)[k]	+ (n=90)	–	Peak cortisol < 500 nmol/L	ECLIA /-	5
Tanriverdi *et al.*(14)	30	+	+	–	+ (n=3)[l]	–	–	Basal cortisol < 193 nmol/L ACTH test: Cortisol < 550 nmol/L	RIA/IRMA	7

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH–deficiency	Assay cortisol/ ACTH	Outcome (%)
Wachter *et al.*(13)	55	+	+	+ (n=NR)[m]	–	–	–	Cortisol below reported reference range (cortisol (16:00 – 20:00 h): 63 – 339 nmol/L)	NR	4

ACS, Automated chemiluminescence system; ACTH, adrenal corticotrope hormone; AUC, area under the curve; CL, confidence limit; CLA, chemiluminometric assay; CRH, corticotrope releasing hormone; ECLIA, electrochemiluminiscence immunoassay; FIA, fluoroimmunoassay; GST, glucagon stimulation test; IA, Immunoassay; IRMA, immunoradiometric assay; ITT, insulin tolerance test; MEIA, microparticle enzyme immunoassay; MSA, magnetic separation assays; NR, not reported; RIA, radio immunometric assay; SST, short synacthen stimulation test

[a] Normal values defined by a group of healthy subjects (n=18)

[b] ACTH test: 250 µg cosyntropin

[c] Cut-off values defined by 31 healthy control subjects

[d] ACTH test: 250 µg Synacthen

[e] Patients with subnormal response to GST (n=23) underwent ITT (n=15) or SST (n=8)

[f] Patients with subnormal basal serum cortisol and ACTH values underwent ITT; not reported how many patients cortisol < 200nmol/L

[g] ACTH test: 250 µg Synacthen

[h] ACTH test: 1 µg Synacthen

[i] Patients with subnormal basal serum cortisol and ACTH values underwent ITT (n=7)

[j] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[k] ACTH test: 250 µg Synacthen

[l] ACTH test: 1 µg Synacthen

[m] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests; CRH test: 100 µg corticotrope releasing hormone

Table 4. Hypothalamus Pituitary Thyroid Axis

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT_4	Outcome (%)
Kelly *et al.*(6)	22	–	+	+	+ (n=22)[a]	TSH < 95% CL according to AUC[b]	ICL/ RIA	5
Lieberman *et al.*(9)	70	–	+	+	+ (n=27)[c]	TSH: 0.49–4.7 mIU/L fT_4: 9.7 – 23.8 pmol/L Insufficient ↑ TSH (5–30 mIU/L); peak TSH not within 60 min	MPIA/ MPIA	15
Bondanelli *et al.*(3)	50	–	+	+	–	Low serum fT_4 with normal or low serum TSH TSH: 0.4–4.2 mIU/L fT_4: 10.3–19.4 pmol/L	ACS/ACS	10
Agha *et al.*(1)	102[d]	–	+	+	–	Low fT_4 without elevation TSH TSH: 0.5 –4.2 mIU/L fT_4: 8–21 pmol/L	FIA/FIA	1
Popovic *et al.* (10)	67	–	+	+	–	NR	IRMA/RIA	4
Aimaretti *et al.* (2)	70	–	+	+	–	fT_4 < 10.29 pmol/L with normal or low TSH	IRMA/RIA	6
Leal-Cerro *et al.*(8)	99	–	+	+	+ (n=NR)[e]	fT_4 ≤ 7.74 pmol/L with normal or low TSH TRH test: TSH peak ≤ 7 mIU/L	RIA/RIA	6

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT4	Outcome (%)
Schneider *et al.*(11)	70	–	+	+	–	fT_4 < 11.97 pmol/L; TSH not elevated	ECLIA/ ECLIA	4
Tanriverdi *et al.*(12)	52	+	+	+	+ (n=NR)[f]	fT_4 < 10.3 pmol/L without appropriate elevation TSH	fT_3, fT_4: RIA TSH: IRMA	6
Herrmann *et al.*(5)	76	+	+	+	–	Low serum fT_4 without appropriate elevation in serum TSH TSH: 0.3–3.0 mIU/L fT_4: 10–25 pmol/L	IA/IA	3
Bushnik *et al.* (4)	64	–	+	+	–	Low serum fT_4 with low or normal TSH Normal reference values: NR	NR	19
Klose *et al.*(7)	104[g]	–	+	+	–	Subnormal fT_4 (<12 pmol/L) with inappropriate low TSH	ECLIA/ ECLIA	2
Tanriverdi *et al.*(14)	30	+	+	+	–	fT_4 < 10.3 pmol/L without appropriate elevation TSH	fT_3, fT_4: RIA TSH: IRMA	0

Table 4. Continued

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT4	Outcome (%)
Wachter *et al.* (13)	55	–	+	+	+ (n=NR)[h]	Criterion for TRH test: NR fT_4: 12–22 pmol/L TSH: NR	NR	6

ACS, Automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; ECL, Electrochemiluminiscence immunoassay; FIA, Fluoroimmunoassay; fT_3: free triiodothyronine; fT_4, free thyroxine; IRMA, immuno radiometric assay; ICL, Immunochemoluminiscense; MPIA, microparticle enzyme immunoassay; NR, not reported; RIA, radio immunoassay; TRH, thyroid releasing hormone; TSH, thyroid stimulating hormone

[a] TRH test: 500 µg

[b] Normal values defined by a group of healthy subjects (n=18)

[c] Abnormal TSH and fT_4 values underwent TRH stimulation test (n=27); 0.5 mg TRH; IV, TSH at T0, 15, 30, 60, 90 min

[d] Cut-off values defined by 31 healthy control subjects

[e] TRH test: 500 µg Protirelin

[f] Not reported how many patients underwent TRH testing and how the test was performed

[g] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[h] Hormonal stimulation tests were performed if abnormatlities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimaltionsts. TRH: 200 µg

Table 5. Hypothalamus pituitary gonadal Axis

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Kelly *et al.* (6)	22	+	+	+	+	+ (n=18)	LH and FSH < 95% CL according to AUC [a] F: increase LH <10 IU/L after GnRH administration T: 10.3 – 36.2 nmol/L E_2: (early follicular phase) 73.4–550.7 pmol/L	LH, FSH: FIA T: RIA E_2: direct assay	23
Lieberman *et al.*(9)	70	+	–	T+	+	+[b] (n=NR)	T below reported reference range (9.7 – 30.5 nmol/L) LH below reported reference rage (M= 2–12 IU/L) Normal response GnRH test: M: peak LH <12 IU/L and increase in LH < 7 IU/L F: peak LH < 10 IU/L and increase in LH < 5 IU/L	T: RIA LH: MEIA	0

Table 5. Continued

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Bondanelli *et al.*(3)	50	+	+	+	NR	–	LH below reported reference range: F: follicular phase 2.5–10 IU/L; menopausal 40–104 IU/L M: 1–10 IU/L FSH below reported reference range: F: follicular phase 2.5–10 IU/L; menopausal 34–96 IU/L M: 1–7 IU/L T below reported reference range (10.1–34.7 nmol/L) E_2 below reported reference range (follicular phase 74–555 pmol/L; menopausal <180pmol/L)	LH, FSH: CLIA T, E_2: RIA	14
Agha *et al.*(1)	102[c]	+	+	T+	+	–	M: low T; inappropriately low LH and FSH Premenopausal F: amenorrhea with low E_2 without ↑ LH and FSH Postmenopausal F: LH and FSH in range of premenopausal	LH, FSH: FIA	12
Popovic *et al.* (10)	67	+	+	T+	+	–	NR	LH, FSH: IRMA T: RIA	9
Aimaretti *et al.*(2)	70	+	+	+	+	–	M : T < 12.1 nmol/L with low or normal FSH and LH Premenopausal F: menstrual disturbances, low E_2 < 73.4 pmol/L with normal or low LH and FSH	LH, FSH: IRMA T,E_2: RIA	11

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Leal-Cerro *et al.*(8)	99	+	+	+	+	+ (n=NR)	M: T < ref val with normal LH and FSH F: menstrual disorder or amenorrhea after TBI, E_2 <0.08 nmol/L normal or low LH and FSH	T: RIA E_2, LH, FSH: FIA	29
Schneider *et al.*(11)	70	+	+	+	+	–	M: T < 12.1 nmol/ without ↑ LH and FSH Premenopausal F = no menses Postmenopausal F = low FSH, LH	All: ECL	29
Tanriverdi *et al.*(12)	52	+	+	+	NR	–	M: T < reference values; normal or ↓LH and FSH Premenopausal F: E_2 < 40.4 pmol/L; inappropriate low LH and FSH Postmenopausal F: LH and FSH in rage of premenopausal women	T: RIA E_2: CLIA LH, FSH: RIA	8
Herrmann *et al.*(5)	76	+	+	+	+	–	M: ↓T; inappropriately low LH and FSH Premenopausal F: amenorrhea ↓E_2 without ↑LH and FSH Postmenopausal F: LH and FSH in premenopausal range	All: IA	17
Bushnik *et al.* (4)	64	–	–	T+	–	–	M: testosterone deficiency: T < 9.0 nmol/L	NR	17
Klose *et al.*(7)	104[d]	+	+	+[e]	+	–	M: T < 10 nmol/L; inappropriate low LH; inhibin B and SHBG Premenopausal F: amenorrhoea/ oligomenorrhoe; low E_2, LH,FSH Postmenopausal F: inappropriate low LH,FSH for age	All: ECL	2

Table 5. Continued

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Tanriverdi *et al.*(14)	30	+	+	+	+	–	M: T < normal (total T < 4.6 nmol/L; free T < 11.5pg/ml); normal or ↓LH, FSH Premenopausal F: E_2 < 40.4 pmol/L; inappropriate low LH, FSH Postmenopausal F: LH, FSH in rage of premenopausal women	T: RIA E_2: CLIA LH, FSH: RIA	0
Wachter *et al.*(13)	55	+	+	T+	–	+ (n=NR) [f]	T below reported reference range (9.7– 27.7 nmol/L) E_2 below reported reference range: (follicular phase 48–709 pmol/L; midcycle peak 316–1828 pmol/L; luteal phase 162–775 pmol/L; postmenopausal < 128 pmol/L) Abnormal response LHRH test: NR	NR	13

ACS, automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; CLIA, chemiluminometric immunoassay; E_2, estradiol; ECL, electrochemiluminiscence; F, female; FIA, fluoroimmunoassay; FSH, follicle stimulating hormone; GHD, growth hormone deficiency; GnRH, gonadotrope releasing hormone; IA, Immunoassay; IRMA, immunoradiometric assay; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; M, male; MEIA, microparticle enzyme immunoassay; MSA, magnetic separation assays; NR, not reported; RIA, radio immunometric assay; T, testosterone

[a] Normal values defined by a group of healthy subjects (n=18)

[b] Patients with abnormalities in basal testosterone levels or menstrual history underwent GnRH; only LH measurements

[c] Cut-off values defined by 31 healthy control subjects

[d] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[e] In case of suspected hypogonadism in men, evaluation was repeated with measurement of inhibin B and SHBG

[f] Hormonal stimulation tests were performed if abnormatlities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimaltions tests; LHRH: 100 µg

Table 6. Prolactin secretion

Study	No. of patients	Basal serum PRL	TRH	Criterion for abnormal PRL secretion	Assay PRL	Outcome (%)
Kelly *et al.* (6)	22	–	+ (n= NR)	Hypoprolactinemia: PRL < 95% CL according to AUC [a]	RIA	0
Lieberman *et al.*(9)	70	+	–	Hyperprolactinemia: M: > 565 pmol/L F: > 1160 pmol/L	MSA	0
Bondanelli *et al.*(3)	50	+	–	Hyperprolactinemie = PRL above reported reference range Hypoprolactinemia = PRL below reported reference range (M: 87 – 696 pmol/L; F: 174 – 1043 pmol/L)	ACS	16
Agha *et al.* (1)	102[b]	+	–	Hyperprolactinemia = basal level PRL > than the locally derived normal assay reference range (M: 83–414 mIU/L; F: 90–523 mIU/L)	FIA	12
Popovic *et al.*(10)	67	+	–	NR	IRMA	12
Aimaretti *et al.*(2)	70	+	–	Hyperprolactinemia: NR	IRMA	6
Leal-Cerro *et al.*(8)	99	+	+[c] (n=NR)	NR	NR	NR
Schneider *et al.*(11)	70	+	–	Hyperprolactinemia: PRL > 1087 pmol	ECLIA	NR

Table 6. Continued

Study	No. of patients	Basal serum PRL	TRH	Criterion for abnormal PRL secretion	Assay PRL	Outcome (%)
Tanriverdi *et al.*(12)	52	+	–	Hyperprolactinemia: basal level greater than the normal reference range (M: 87 –1783 pmol; premenopausal F: 122–1261 pmol; postmenopausal F:78–870 pmol)	RIA	8
Herrmann *et al.*(5)	76	+	–	Hyperprolactinemia: PRL above reported reference range (M:870 pmol; F: <1087 pmol)	IA	3
Bushnik *et al.*(4)	64	–	–	–	–	–
Klose *et al.* (7)	104[d]	+	–	Hyperprolactinemia: PRL > 510 mIU/L	ECLIA	NR
Tanriverdi *et al.*(14)	30	+	–	Hyperprolactinemia: basal level greater than the normal reference range (M: 87 –1783 pmol; premenopausal F: 122–1261 pmol; postmenopausal F: 1.8–20 ng/ml)	RIA	NR
Wachter *et al.*(13)	55	+	+[e] (n=NR)	NR	NR	NR

AUC, area under the curve; ACS, automated chemiluminescence system; CL, confidence limit; ECLIA, Electrochemiluminiscence immunoassay; FIA, Fluoroimmunoassay; IA, Immunoassay;
IRMA, immunoradiometric assay; MSA, magnetic separation assays; NR, not reported; PRL, prolactin; RIA, radio immunometric assay; TRH, thyroid releasing hormone
[a] Normal values defined by a group of healthy subjects (n=18)
[b] Cut-off values defined by 31 healthy control subjects
[c] TRH test: 500 ug
[d] 30 age- and BMI-matched healthy controls all underwent pituitary testing
[e] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests. TRH: 100 µg

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Chapter 3

Low prevalence of hypopituitarism after traumatic brain injury – a multi-center study

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Abstract

Objective: Hypopituitarism after traumatic brain injury (TBI) is considered to be a prevalent condition. However, prevalence rates differ considerably among reported studies, due to differences in definitions, endocrine assessments of hypopituitarism, and confounding factors, like timing of evaluation and the severity of the trauma.

Aim: To evaluate the prevalence of hypopituitarism in a large cohort of TBI patients after long-term follow-up using a standardized endocrine evaluation.

Study design: Cross-sectional study

Patients and Methods: We included 112 patients with TBI, hospitalized for at least 3 days and a 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). Clinical evaluation included quality of life questionnaires.

Results: We studied 112 patients (75 males), with median age 48 yr, and mean BMI 26.7±4.8 kg/m^2. Mean duration of hospitalization was 11 days (3–105) and 33% had a severe trauma (Glasgow Coma Scale < 9) after TBI. The mean duration of follow-up was 4 (1–12) years. Hypopituitarism was diagnosed in 5.4% (6/112) of patients: severe GH deficiency (n=4), hypogonadism (n=1), adrenal insufficiency (n=2). Patients diagnosed with pituitary insufficiency had significantly higher BMI (P =0.002).

Conclusion: In this study, the prevalence of hypopituitarism during long-term follow-up after TBI was low. Prospective studies are urgently needed to find reliable predictive tools for the identification of patients with a significant pre-test likelihood for hypopituitarism after TBI.

Introduction

Traumatic brain injury (TBI) is common and an important cause of death, especially among adolescents in developed countries. The last decade, pituitary insufficiency has emerged as an important sequel following TBI, potentially influencing short- and long-term morbidity. After TBI, many 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) (1–4). Consequently, pituitary insufficiency following TBI may contribute to the problems reported by these patients (4). This condition is important to identify since it can be treated by hormone replacement therapy resulting in improved QoL (3;5).

However, the actual prevalence of hypopituitarism after TBI in an unselected population is subject for debate. The available cohort studies studying the prevalence of pituitary insufficiency report percentages ranging from 15 to 90% (6–18). There are several explanations for this remarkably wide range in reported prevalences, including differences in inclusion criteria, differences in duration of follow-up since TBI (short *vs* long term follow-up) and the use of different tests, different assays and different cut-off values (19).

Therefore, the aim of our study was to evaluate the prevalence of hypopituitarism in a large cohort of TBI-patients after long-term follow-up, using standardized endocrine evaluation including golden standard tests. The secondary aim was to assess QoL and the contribution of hypopituitarism on QoL.

Patients and methods

Study protocol

We performed a multicenter study in 5 hospitals across the Netherlands (Leiden University Medical Center; Academic Medical Center, Amsterdam, St. Elisabeth Hospital, Tilburg; Isala Clinics, Zwolle; Medical Spectrum Twente, Enschede). Eligible patients were selected from electronic registries of the departments of neurology using the following inclusion criteria: confirmed diagnosis of TBI and hospitalization for at least three days for head injury at least one year prior to endocrine evaluation (to exclude possible hormone alterations mimicking pituitary insufficiency in the early post trauma period), age 18–70 yrs. Exclusion criteria were: medical or psychological problems (not related to TBI) that could disturb interpretation of results, including drug- or alcohol abuse, previously known hypothalamic- or pituitary dysfunction or history of cranial irradiation or pregnancy. Details on trauma severity were derived from the medical records. The Glasgow Coma Scale (GCS) at hospitalisation defined trauma severity. A GCS 13–15 indicates mild trauma, between 9–12 moderate trauma, and < 9 severe trauma (20;21). Ethical approval was obtained by the Medical Ethics Committees of all centers and all patients gave written informed consent.

Patients

A total of 2350 potential patients were retrieved from the electronic databases that had been diagnosed with TBI. The electronic patient records of these patients were retrieved in the departments of neurology of all participating hospitals. However, 1960 patients did not meet the abovementioned inclusion criteria and were excluded. The remaining 390 patients were invited to participate, of whom 278 patients could not be included for various reasons: not willing to participate without giving any reason, not meeting the inclusion criteria (either 2 days of hospitalization, drug or alcohol abuse, or medication that could not be stopped) or were loss to follow-up. Ultimately, we included a total of 112 patients in the study (Figure 1).

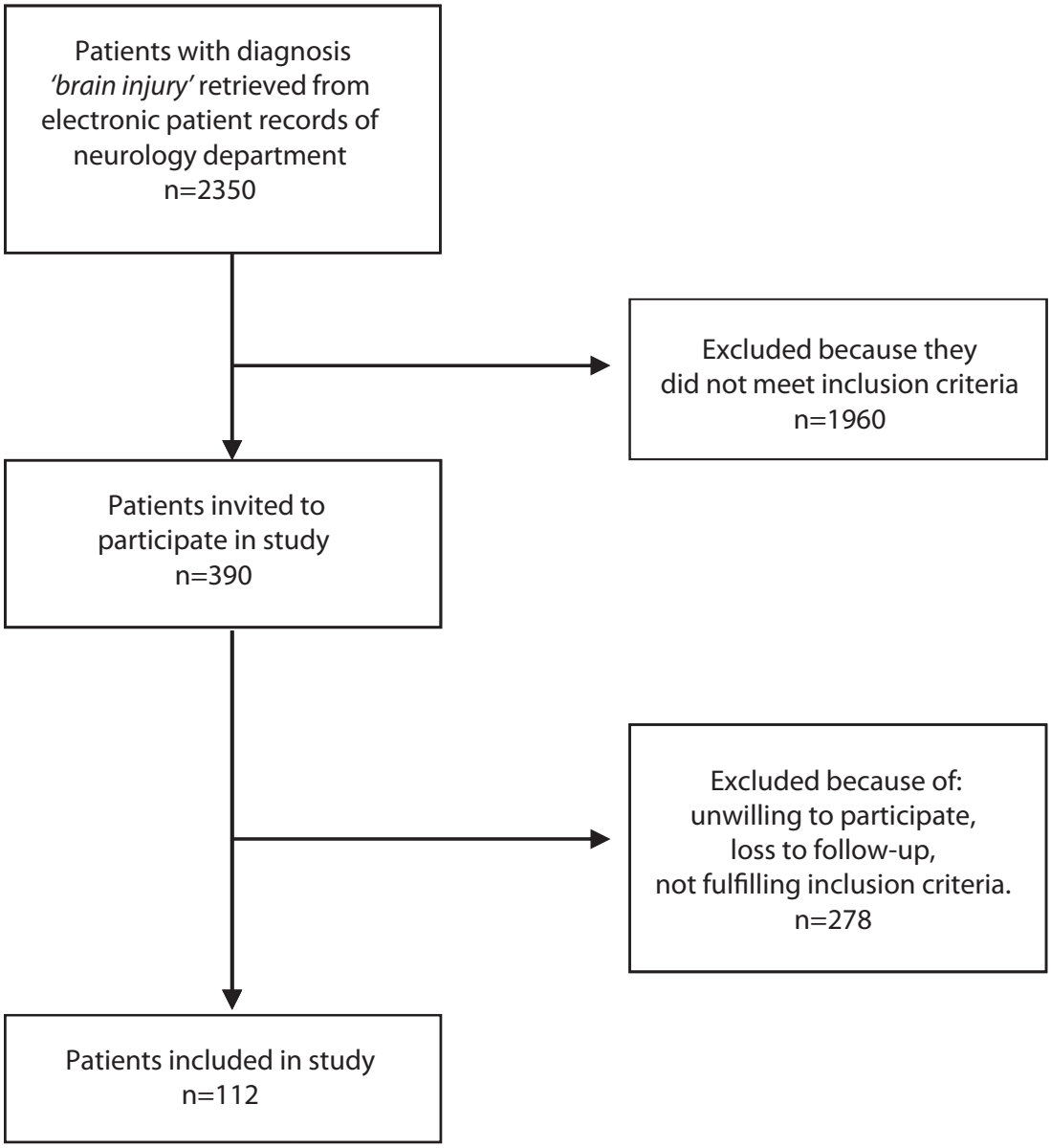

Figure 1. Flow chart of inclusion of patients

Endocrine evaluation

Blood was sampled for assessment of basal and stimulated hormone concentrations between 08.00 and 09.00h A.M. after an overnight fast. All patients rested 30 min prior to testing after insertion of an indwelling catheter in a large forearm vein. Baseline samples were drawn for analyses of cortisol, free thyroxine (fT_4), TSH, testosterone (men) estradiol (E_2; women), LH, FSH, prolactin (PRL), GH and IGF-I. Oral contraceptives were discontinued for at least 6 weeks before testing.

The hypothalamic-pitutiary adrenal (HPA) and GH-IGF-I axes were evaluated with an insulin tolerance test (ITT), unless contraindicated, or alternatively by ACTH/CRH and GHRH-stimulation tests. An ACTH-test (1 or 250μg Synacthen iv, Novartis Pharma BV, Arnhem, the Netherlands), with measurement of cortisol at T= -5, 30 and 60 min, was performed routinely in all patients prior to the ITT to ensure sufficient adrenal function. ITT was performed by administering soluble insulin intravenously (0.10 U/kg, Actrapid, Novo, Alphen aan den Rijn, The Netherlands) to induce hypoglycaemia (glucose < 2.2 mmol/L). Cortisol, ACTH, GH and glucose levels were measured at T = -15, 0, 15, 30, 45, 60 and 90 min. Peak values of GH of 3 μg/L and cortisol of >500 nmol/L were considered to reflect sufficient pituitary GH and ACTH function. If ITT was contraindicated, a GHRH-arginine test was conducted to evaluate GH secretory reserve. Patients received 1 μg/kg GHRH (Ferring BV, Hoofddorp, the Netherlands) and 500 mg/kg arginine with a maximum of 30 gr. GH levels were measured at T = –15, 0, 30, 45, 60, 75 and 90 min. BMI adjusted cut-off values of 11.5 μg/L (< 25 kg/m^2), 8.0 μg/L (25-30 kg/m^2), and 4.2 μg/L (> 30 kg/m^2) were used (22). For the evaluation of the HPA axis when ITT was contraindicated, the response to ACTH-stimulation was considered and an additional CRH-stimulation test was performed in selected cases (Table 2).

Assays

GH was measured in participating centers using in-house assays. The measurement of GH has been harmonized in the Netherlands (23) and in all centers, GH was calibrated against the WHO-IRP 98/574 (1 μg/L = 3.0 mU/L). IGF-I measurement was centralized at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Göteborg, Sweden using a chemiluminescence immunoassay (DPC, Immulite 2500 system, Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra- and inter-assay coefficients of variation (CVs) were 4 and 11%. Reference values based on Brabant *et al.* (24) were used. With these IGF-I values IGF-I SD scores were calculated.

The participating centers used the following in house assays and cut-off values:

Leiden University Medical Center, Leiden: Cortisol, fT_4, TSH, LH, FSH and prolactine blood levels were measured by electrochemoluminescent

immunoassay (ECLIA), using a Modular E170, (Roche Diagnostics, Mannheim, Germany). The maximal inter-assay coefficient of variation was 5.0%. ACTH, GH and IGF-I were determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay coefficient of variation was between 5.0 and 10.0%. Glucose levels were measured using a Modular P800 (Roche Diagnostics Mannheim, Germany) (CV is 3%). For measurement of estradiol levels a radioimmunoassay (RIA, Orion Diagnostica, Espoo, Finland) was used (CV is 6% at 70 pmol/L). The estradiol detection limit was 20 pmol/L. Testosterone was measured using a RIA (Siemens Healthcare Diagnostics, Deerfield IL, USA). (CV is 20% at 1.0 nmol/L and 12% at 14 nmol/L) The detection limit was 0.2 nmol/L.

Academic Medical Center, Amsterdam: Plasma LH, TSH and FSH were analysed by an automated assay on the E170 of Roche (Roche, Mannheim, Germany). The maximal intra- and inter-assay variations were < 5%. Plasma fT_4, PRL and GH were analyzed by fluoroimmunoassay (Delfia, Perkin Elmer, Waltham, MA, USA) using the Delfia 1232 Fluorometer (Perkin Elmer). The maximal intra- and inter-assay CVs were 5.1 and 6.8% for fT4, 3.4 and 5.3% for PRL, and 3.8 and 6.2% for GH, respectively. Testosteron was analysed by an in-house RIA. The maximal intra- and inter-assay CVs were 11.8 and 12.8% respectively. Cortisol was analysed by chemoluminiscence assay using the Immulite 2000 (Siemens, Healthcare Diagnostics). The maximal intra- and inter-assay CVs were 5.5 and 8.3% respectively. E_2 was measured by RIA (Siemens Healthcare Diagnostics). The intra- and inter-assay CVs were < 20% (low level) and maximal at 8.6% (medium level).

St. Elisabeth Hospital, Tilburg and Isala Clinics, Zwolle: Plasma TSH, fT_4, PRL, LH, FSH, testosterone and E_2 were analyzed by ECLIA (Modular Analytics E170, Roche, GmbH). The maximal intra- and inter-assay CVs as specified by the manufacturer were as follows: TSH, 3.0 and 7.2%; fT_4, 2.0 and 4.8%; PRL, 1.7 and 2.0%; LH, 1.2 and 2.2%; FSH, 2.8 and 4.5%; testosterone, 2.8 and 3.2%; and E_2, 3.6 and 3.9%. GH was analyzed by a solid-phase, two-site chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics). Intra- and inter-assay CVs given by the manufacturer were 4.2 and 6.6% respectively.

Medical Spectrum Twente, Enschede: Plasma GH, LH, FSH, PRL, testosterone, and E_2 levels were analyzed by solid-phase, two-site

chemiluminescent immunoassays (Immulite 2000, Siemens Healthcare Diagnostics). The maximal intra- and inter-assay CVs were as follows: GH, 4.2 and 6.6%; LH, 3.6 and 6.7%; FSH, 2.9 and 4.1%; PRL, 3.6 and 7.4%; testosterone, 10.0 and 10.3%, and E_2, 7.8 and 11.0%. Cortisol was analyzed by a solid-phase, competitive chemiluminescent immunoassay (Immulite 2000, Siemens). Intra- and inter-assay CVs were 7.4 and 9.4% respectively. Plasma TSH and fT_4 were analysed by ECLIA (Modular Analytics E170, Roche, GmbH). Intra- and inter-assay CVs were: 3.0 and 7.2% for TSH and 2.0 and 3.6% for fT_4.

Quality of life assessment

To assess QoL the following questionnaires were used:

Hospital Anxiety and Depression Scale (HADS) – The HADS questionnaire consists of 14 items pertaining to anxiety and depression, measured on a four-point scale. The scores for the two subscales anxiety and depression range from 0–21 and the total score from 0–42. A high score indicates more severe anxiety or depression (25).

Nottingham Health Profile (NHP) – The NHP questionnaire features 38 yes/no questions subdivided in six subscales, *i.e.* energy, pain, emotional reaction, sleep, physical ability and social isolation. Scores of the subscales are valued in a range from 0–100. The total score is the mean of all subscales. A high score indicates a worse QoL (26;27).

Multidimensional fatigue index (MFI-20) – The MFI-20 questionnaire contains 20 statements to assess fatigue, measured on a five-point scale. The scores of the five subscales general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue vary from 0 to 20. A high score indicates more fatigue experienced (28).

Short Form-36 (SF-36) – The SF-36 consists of 36 statements or questions evaluating general well-being during the previous 30 days. Scores of the nine subscales physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, pain, general health perception and health change are expressed in a 0–100 scale. Higher scores indicate a better QoL (29;30).

Statistics

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc.,Chicago, IL, USA). All data were presented as mean±SD,

unless mentioned otherwise. The analysis comprised the comparison of the results between patients with and without pituitary insufficiency.

Groups were compared using an independent-samples t-test. A χ^2-test was used in case of categorical data. To analyse QoL the groups were compared using univariate analysis of variance (ANOVA) with gender and GCS as fixed factors and age as covariate when appropriate. Factors influencing QoL were explored using a Pearson correlation. A P-value of <0.05 was considered to be statistically significant.

Results

Patient demographics

We included 112 patients (75 males) with a median age of 48 (range 19–69) years (Table 1). Patients were evaluated 1–12 years after trauma (median 3 years). The median duration of hospitalization after TBI had been 11 (3–105) days. BMI was 25 (18–43) kg/m^2. The causes of TBI had been traffic accidents (51%), fall (38%), violence (5%), and sport- or work related accidents (6%), respectively. A total of 36 patients (32%) had been diagnosed with a severe trauma and 56% of the patients (n=60) had a mild trauma, in 4 patients the GCS was not clear from the medical records.

Table 1. Baseline characteristics

	TBI Patients (n=112)
Gender (M/F)	75/37
Age (years)	48 (19–69)
BMI (kg/m^2)	26.7 ± 4.8
GCS:	
Mild (%)	57%
Moderate – Severe (%)	43%
Time since TBI (years)	4.2 ± 3.3
Duration of hospitalization (days)	11 (3–105)

BMI, body mass index; F, female; M, male; TBI, traumatic brain injury
Data are presented as mean±SD or median (range).

Endocrine evaluation

Any pituitary insufficiency was diagnosed in only 6/112 patients, resulting in a prevalence rate of 5.4%. Patients with and without pituitary insufficiency were comparable in age and gender, but in patients diagnosed with pituitary insufficiency BMI was significantly higher (P = 0.02). Trauma severity, the duration of follow-up, and duration of hospitalization were not different between the two groups.

GH-IGF-I axis: The ITT was used in 80% of the patients (90/112) for the evaluation of GH secretory reserve (Figure 2). Because of contra-indications (epilepsy (n=6), ischemic heart disease or rhythm disorders (n=3), other (n=13)), the remaining patients were tested using combined GHRH-arginine stimulation. Severe growth hormone deficiency (GHD) was diagnosed in 3.6% of the patients (2M/2F, Table 2).

HPA axis: At baseline, all patients initially were screened with basal morning cortisol levels and a 1 or 250μg ACTH-test to evaluate adrenal function. Subsequently, 90 patients were tested by ITT (Figure 2). In the remaining 22 patients the HPA axis was assessed by the results of basal cortisol and the ACTH-test. In addition, 2 patients (diagnosed with other pituitary insufficiencies) were tested also by a 100 μg CRH test.

ACTH deficiency was diagnosed in 1.8% of patients (2/112) by insufficient cortisol responses during ITT (Table 2).

Gonadal axis: Hypogonadism was diagnosed only in one male patient (0.9%).

Thyroid axis: We did not diagnose any patient with thyroid insufficiency.

Quality of life

There were differences in QoL between patients diagnosed with and without pituitary insufficiency. Patients with pituitary insufficiency scored worse on almost all subscales of the QoL questionnaires. More specifically, they scored significantly worse on the subscale 'Depression' of the HADS ($P = 0.05$), on the subscale 'Social isolation' of the NHP ($P = 0.02$), on the subscale 'Reduced activity' of the MFI-20 ($P = 0.027$) and on the subscale 'General health perception' of the SF-36 ($P = 0.016$) (data not shown).

Table 2. Characteristics of patients diagnosed with any pituitary insufficiency

Patient no.	Sex	Age (years)	BMI (kg/m²)	GCS score	Time since TBI (years)	Dynamic test		IGF-I SDS	Peak GH (µg /L)	Peak cortisol (nmol/L)	Deficiency
						GH axis	*HPA axis*				
1	M	65	32.2	3	3	ITT	ITT	-1.0	4.0	425	Cortisol
2	M	64	29.7	7	9	GHRH-arg	ACTH,CRH	-2.4	2.8	508	GH
3	M	41	32.8	3	4	GHRH-arg	ACTH	-0.2	9.9	590	Testosterone
4	M	27	23.5	3	10	GHRH-arg	ACTH, CRH	-0.7	9.4	757	GH
5	F	28	29	15	1	ITT	ITT	1.2	1.9	790	GH
6	F	23	32.3	14	3	ITT	ITT	-0.6	2.4	395	GH, Cortisol

BMI, body mass index; CRH, corticotropin releasing hormone; F, female; GCS, Glasgow Coma Scale; GH, growth hormone; GHRH, growth hormone releasing hormone; HPA, hypothalamic pituitary adrenal axis; ITT, insulin tolerance test; M male

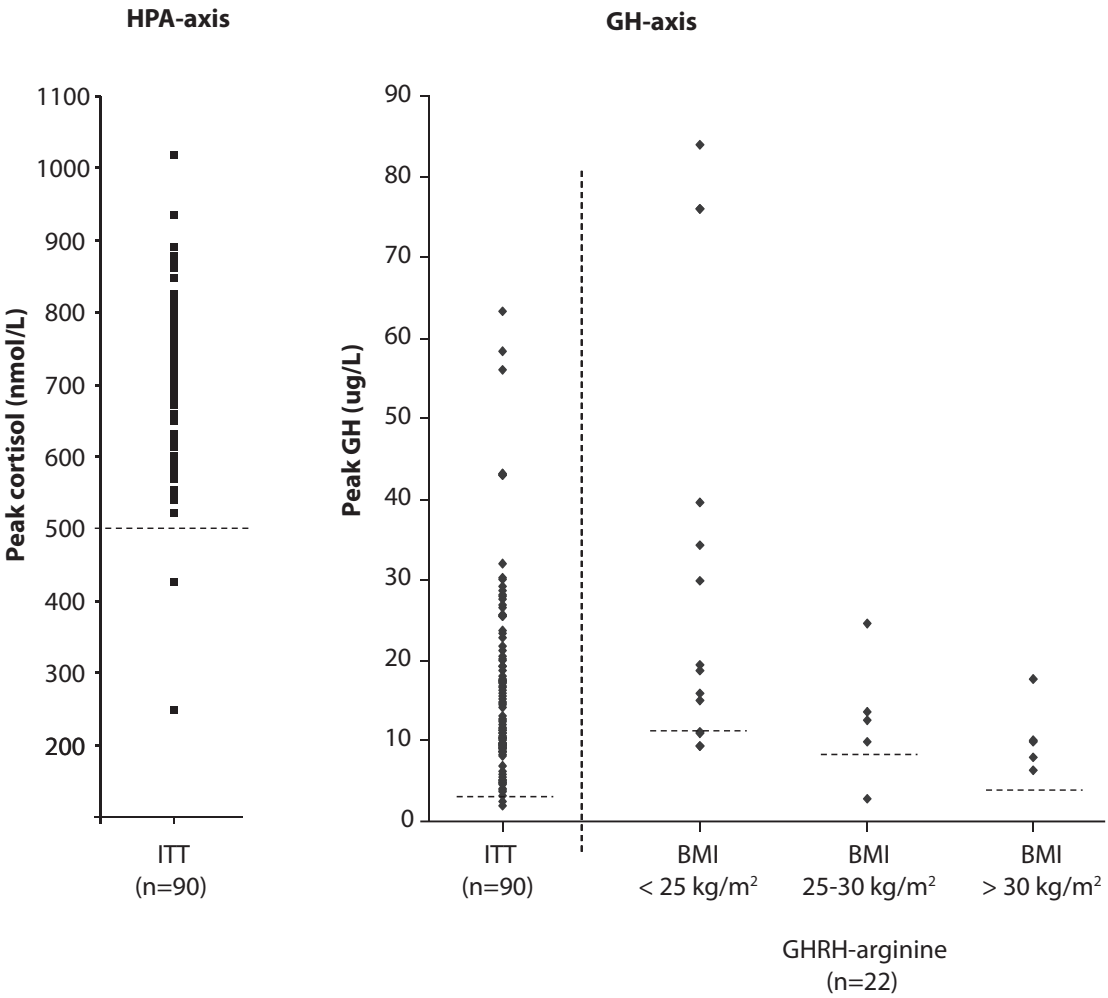

Figure 2. Test results of the stimulation of GH and cortisol secretory reserves during ITT or combined GHRH-arginine test. The dotted horizontal line represents the cut-off value used to define an insufficient response.

Discussion

This study demonstrates that the prevalence of hypopituitarism after TBI in a large patient cohort after long-term follow-up is low. Using a standardized evaluation that included the gold standard test for the evaluation of GH and cortisol secretory reserves in the majority of the patients, we found a prevalence of only 5.4% of any pituitary insufficiency.

This prevalence of hypopituitarism is much lower compared with the prevalence rates reported in the majority of the previous studies (15–90%) (6–18). This might be explained by the use of different endocrine tests and cut-off values (19). For example, comparable low prevalences of hypopituitarism was found in another study that also used the ITT for screening (15). In addition, when using the combined GHRH-arginine test without BMI-adjusted cut-off values the prevalence of severe GHD varied between 8 and 20%(19). A higher BMI is associated with a decreased GH response to GH stimulation tests (22). If BMI-adjusted cut-off values are not used, a higher proportion of patients will be classified as GHD. In addition, age adjusted cut-off values have recently been reported for the GHRH-arginine test (31).

Differences in the duration of follow-up between TBI and endocrine assessment may also play an important role. Hormone alterations mimicking pituitary insufficiency can be present in the acute phase after trauma. In general, these transient effects are almost exclusively reported only within the first six months after TBI (15;32). Therefore, assessment of the function of pituitary axes within this timeframe may result in higher prevalence rates of hypopituitarism. To avoid this bias we decided to assess patients at least one year after the trauma, as suggested in the consensus guidelines for the evaluation and diagnosis of patients with possible GHD (33). In addition to the time interval between TBI and endocrine assessment, the severity of trauma may affect the prevalence rate of pituitary insufficiency (15;34). As shown by Klose *et al.* (34), increased trauma severity increases the risk of pituitary insufficiency. This may result in higher prevalence rates when patients with a more

severe degree of trauma are included. Conversely, prevalence rates of hypopituitarism may decrease when patients with only minor traumas are included (35).

It is important to note that in our study, only a minority of the screened patients fulfilled our inclusion criteria, of which 28.7% participated. Therefore, by definition, we investigated a pre-selected cohort, which may have affected the results, and, therefore, our conclusions cannot simply be extrapolated to all TBI patients. However, we were able to evaluate the most important clinical characteristics in the majority of the patients (79%) who did not participate and found no differences in age during TBI, gender, trauma severity and duration of hospitalization when compared to those that finally did participate (data not shown). This makes a possible bias as a result of pre-selection less likely.

Thus, according to our results, pituitary insufficiency may be a rare complication of TBI in patients evaluated at least one year after TBI. Intriguingly, comparable low prevalence rates were found in another study that also used the ITT to evaluate cortisol and GH secretory reserve (32). However, it should be taken into account that there is a high incidence of TBI in the population probably translating in still a high prevalence of posttraumatic hypopituitarism on a population-based level. Besides pre-selections of patients, the use of different tests with different cut-off values has contributed to the differences and large variations in the prevalence rates found in previous studies (19). Our results accentuate that we urgently need consensus for a more uniform and protocol endocrine evaluation after TBI. More importantly, we urgently need prospective studies to find reliable predictors that enable the identification of patients with a significant pre-test likelihood for hypopituitarism. This is of paramount importance, because the presence of pituitary failure, even in a small proportion of patients, is potentially treatable, may be lifesaving, and is likely to significantly ameliorate quality of life (3;5).

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Chapter 4

The use of an early postoperative CRH test to assess adrenal function after transsphenoidal surgery for pituitary adenomas

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Abstract

Purpose: Transsphenoidal surgery (TS) is the treatment of choice for many pituitary tumors. Because TS may cause pituitary insufficiency in some of these patients, early postoperative assessment of pituitary function is essential for appropriate endocrine management. The aim of our study was to evaluate the clinical relevance of the CRH stimulation test in assessing postoperative pituitary-adrenal function.

Methods: We performed a retrospective analysis of 144 patients treated by TS between January 1990 and November 2009, in whom a CRH test and a second stimulation test was performed to assess adrenal function during follow-up. Patients with Cushing's disease were excluded. Hydrocortisone substitution was started if peak cortisol levels were < 550nmol/L.

Results: The cortisol response was insufficient in 42 (29%) and sufficient in 102 patients at the postoperative CRH test. Thirteen of 42 (30%) demonstrated a normal cortisol response during a second cortisol stimulation test. In 75 of the 102 patients with a sufficient response to CRH repeat testing revealed an insufficient cortisol response in 14 patients (14%). All but one had concomitant pituitary hormone deficits. There were no cases of adrenal crises during follow-up. Additional pituitary insufficiency was significantly more present ($P < 0.001$) in the group of patients with an abnormal response to CRH directly after surgery.

Conclusion: In this study a substitution strategy of hydrocortisone guided by the postoperative cortisol response to CRH appeared safe and did not result in any case of adrenal crises. However, the early postoperative CRH test does not reliably predict adrenal function after TS for pituitary adenomas in all patients, and retesting should be strongly considered.

Introduction

Transsphenoidal surgery (TS) is the treatment of choice for many pituitary tumors. TS may result in (additional) pituitary insufficiency in some of these patients (1–3). Therefore, accurate assessment of pituitary function is essential for appropriate management of postoperative patients after TS. In this respect, evaluation of the pituitary-adrenal axis is clinically relevant to assess the need for hydrocortisone replacement therapy at discharge.

The insulin tolerance test (ITT) is considered to be the gold standard for the evaluation of secondary adrenal insufficiency (4;5). Because there are contraindications for ITT in some patients, the CRH test, the metyrapone test or the ACTH stimulation test can be used as alternative dynamic tests to assess adrenal function (6–8). However, there is no international consensus for postoperative testing after pituitary surgery. We performed a structured literature search for articles that 1) evaluated the postoperative strategy for evaluation of adrenal function and 2) use of the CRH test to evaluate the pituitary-adrenal axis in postoperative patients after TS for pituitary adenomas, excluding manuscripts on patients with Cushing's disease. However, specific data on this topic are hardly available. Moreover, studies that compared CRH test and other dynamic test in other situations (*i.e.* in patients with (suspected) hypothalamic-pituitary insufficiency not specifically related to surgery) reported contradictory results (8;9). Therefore, at our center we developed a strategy for evaluation of patients after pituitary surgery in 1990 using the CRH test as the first postoperative test.

The aim of the present study was to assess the clinical relevance of the CRH stimulation test, as a part of this evaluation strategy, in assessing pituitary-adrenal function after TS. We performed a retrospective analysis of all patients treated by TS between January 1990 and November 2009, in whom a CRH test and a second stimulation test was performed to assess adrenal function during follow-up in non-Cushing patients.

Patients and methods

Study design

We performed a retrospective chart review of all patients, who had been treated by TS in the Leiden University Medical Center between January 1990 (when human CRH (hCRH) became available for routine clinical use) and November 2009. Patients with available data on a postsurgical CRH test, who also had a second (confirmation) test of adrenal function during follow-up were included. We excluded patients on high dose glucocorticoids, reoperation, postoperative cranial radiotherapy, and patients treated by TS for Cushing's disease.

The Medical Ethics Committee of our hospital declared that no formal ethical approval and written informed consent was needed for this anonymous retrospective chart review.

Endocrine assessment

According to the postoperative protocol, which has been implemented in our hospital, the pituitary-adrenal axis is assessed by CRH test, 7–10 days after surgery. The CRH test is performed after an overnight fast, after withdrawal of hydrocortisone for 24 hours, using 100 μg CRH (Corticoliberine, Ferring Farmaceuticals Hoofddorp, the Netherlands). Venous blood samples for measurement of ACTH and cortisol concentrations are collected at -15, 0, 15, 30, 45 and 60 minutes after infusion. A peak plasma cortisol of ≥ 550 nmol/L is considered to reflect a normal response (10;11).

In case of insufficient cortisol responses to CRH, hydrocortisone is prescribed (20 mg/day, divided in 3 doses). During follow-up, the treating endocrinologist decided on re-testing of the adrenal function. For the assessment of the HPA axis during follow-up either basal serum cortisol levels or a stimulation test was used. The ITT was performed after an overnight fast by intravenous administration of insulin (0.10 U/kg, Actrapid, Novo Nordisk Farma, Bagsvaerd, Denmark) to induce adequate hypoglycemia, defined as nadir glucose levels

< 2.2 mmol/L. Blood was collected for measurement of cortisol, ACTH and GH at -15, 0, 15, 30, 45, 60, 90 and 120 minutes after i.v. administration of insulin. Peak values of GH > 9 mU/L (corresponding with 3 µg/L) and cortisol of ≥ 550 nmol/L were considered to reflect normal pituitary function of GH and ACTH secretion (4;12–15).

For the ACTH test 1 µg Synacthen (Novartis Pharma, Arnhem, The Netherlands) was administered i.v. and cortisol levels were measured at -15, 0 and 30 minutes after infusion. A peak cortisol value of ≥ 550 nmol/L was considered to reflect normal adrenal reserve (16–18). In addition, a basal serum cortisol concentration of > 550 nmol/L was considered to reflect normal adrenal function (9).

In some patients a metyrapone test was used as a second test to assess pituitary adrenal function. Metyrapone (30 mg/kg, Metopiron, Novartis Pharma B.V., Arnhem, the Netherlands) was administered orally at midnight. The next morning postabsorptive blood samples were obtained for measurement of 11-deoxycortisol, cortisol and ACTH levels. A cut-off value for 11-deoxycortisol of 200 nmol/L was used to define normal adrenal function (6;19;20).

Assays

Between 1986 and 1994, a fluorescence energy-transfer immunoassay Syva-Advance (Syva Company, Palo Alto, CA) was used, with an interassay variation coefficient of 3.6 – 6.1% and a detection limit of 50 nmol/L. From 1994, cortisol was measured by fluorescencepolarization assay on a TDx (Abbott Laboratories, Abbott Park, IL). The interassay variation coefficient is 5–6% above 500 nmol/L and amounts to 12% under 200 nmol/L. The detection limit is 20 nmol/L. The methods correlated well with each other, and therfore no correction factors were introduced for follow-up of patients. ACTH was determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay coefficient of variation (CV) was between 5.0 and 10.0%. During the insulin tolerance test glucose levels were measured using a Modular P800 (Roche Diagnostics, Mannheim, Germany).

For the measurement of 11-deoxycortisol a radioimmunoassay (RIA) of Diasource (previously Biosource Europe, Nivelles, Belgium) was used. CV was approximately 11%.

Free T_4, TSH, LH, FSH and prolactine blood levels were measured by electrochemoluminescent immunoassay (ECLIA), using a Modular E170, (Roche Diagnostics, Mannheim, Germany). The maximal inter-assay CV for these hormones was 5.0%. ACTH, GH and IGF-I were determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay CV was between 5.0 and 10.0%. Glucose levels were measured using a Modular P800 (Roche Diagnostics Mannheim, Germany) (CV is 3%). For measurement of estradiol levels a RIA (Orion Diagnostica, Espoo, Finland) was used (CV is 6% at 70 pmol/L). The estradiol detection limit was 20 pmol/L. Testosterone was measured using a RIA (Siemens Healthcare Diagnostics, Deerfield IL, USA). (CV is 20% at 1.0 nmol/L and 12% at 14 nmol/L). The detection limit was 0.2 nmol/L.

Statistical analysis

PAWS for Windows version 17.0 (SPSS Inc. Chicago, IL) was used to perform data analysis. Data were presented as mean ± SD unless otherwise mentioned. To evaluate the difference between peak cortisol of the direct postsurgical CRH test and the confirmation test during follow-up we used a paired t-test. A χ^2-test was used to evaluate the difference in prevalence of additional pituitary insufficiency in patients diagnosed with or without adrenal insufficiency based on the CRH stimulation test. The level of significance was set at $P \leq 0.05$.

Results

Patients

Between January 1990 and November 2009, 291 patients were treated by TS for non-functioning pituitary adenomas; NFA (n=160), GH-producing adenomas (n=96), prolactinomas (n=16) or other pituitary tumors (n=19) (Figure 1). A CRH test directly following surgery was not performed in 82 patients for several reasons (pituitary insufficiency prior to surgery n=29, follow-up in outpatient clinic n=11, use of corticosteroids surrounding surgery n=5, other stimulation test directly after surgery n=7, other n=30). Consequently, a CRH test was performed in 209 postoperative patients after TS. In 65 of these 209 patients, there was no additional adrenal test performed in follow-up between TS and referral for postoperative radiotherapy (n=24), repeat surgery (n=5), or death of the patient (n=10), or due to follow-up in another hospital (n=17) and lost to follow-up (n=9). Therefore, 144 patients were finally included in this study. Baseline characteristics of these 144 patients are presented in Table 1.

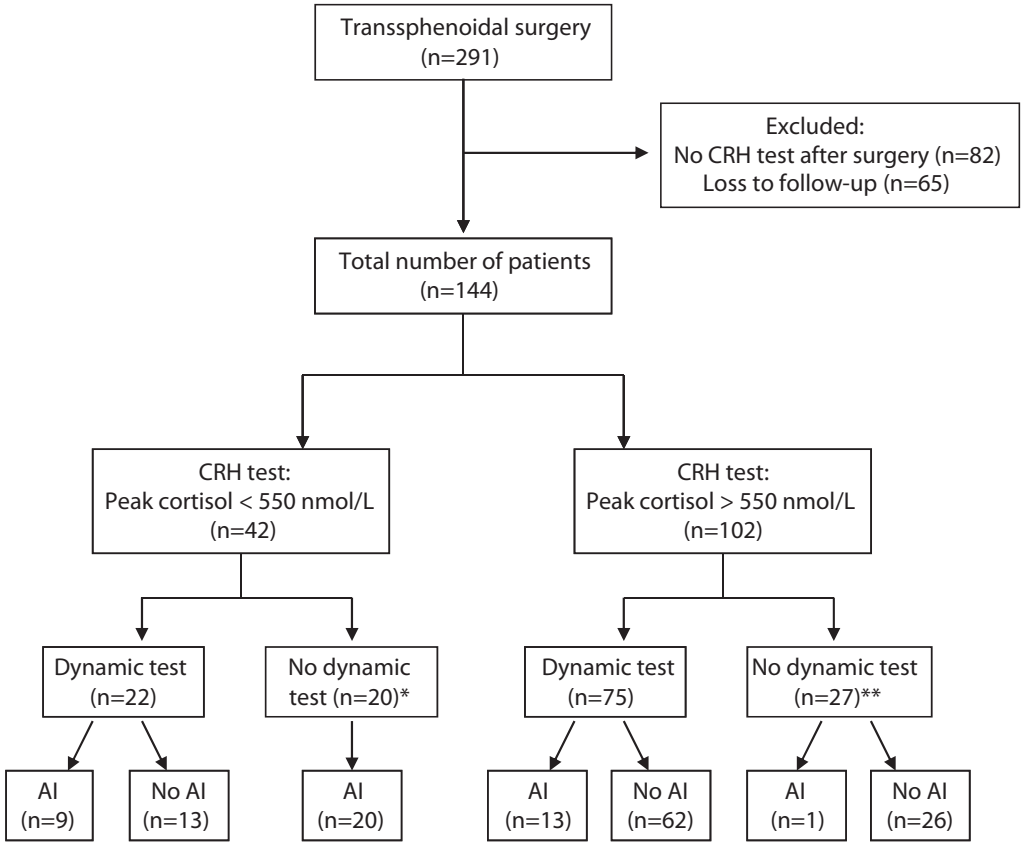

Figure 1. Flow-chart of patient selection and follow-up. *AI* = adrenal insufficiency.
*pre-existent panhypopituitarism before or immediately after surgery (n=12), pre-existent isolated severe adrenal insufficiency before surgery (n=4) or very low basal serum cortisol concentrations (mean 10 nmol/L) during follow-up after surgery (n=4).
**basal serum cortisol levels > 550 nmol/L (n=12), normal urine cortisol levels (n=3), short follow-up between repeated surgery or additional radiotherapy (n=2), and follow-up < 1 year (n=2) or unspecified reasons (n=7), basal serum cortisol < 110 nmol/L (n=1)

Table 1. Baseline characteristics total population

Baseline characteristics	**Number of patients (n=144)**
Gender (M/F)	71/73
Age (years)	50 (15–83)
Diagnosis (n):	
NFA	70
Acromegaly	63
Prolactinoma	6
Other pituitary tumors	5
Time between CRH test and confirmation test (months)	25.5 (2days*–219 months)
Confirmation test (n=97):	
ITT	55
CRH	16
ACTH stimulation test	21
Metyrapone test	5

* Basal serum cortisol was low, however CRH test peak cortisol 0.61; 2 days after CRH test a metyrapone test was performed

Patients with a decreased postoperative cortisol response to CRH (n=42)

The peak levels of cortisol during the postoperative CRH test classified 42 of the 144 patients with pituitary-adrenal insufficiency (peak cortisol < 550 nmol/L) (Figure 1). In 22 of these 42 patients with a median peak cortisol response to CRH of 480 (30–547) nmol/L, a second stimulation test was performed during follow-up: ITT (n=8), ACTH stimulation test (n=8), CRH stimulation test (n=5) and metyrapone test (n=1). These confirmation tests were performed with a median interval of 27.5 (1–139) months after the initial postoperative CRH test. Based on this repeat test, 9 of these 22 (41%) patients had persistent adrenal insufficiency [median initial cortisol response 356 (30–547) nmol/L; median cortisol response confirmation test 219 (3–514) nmol/L}, who received hydrocortisone (HC) replacement and 13 (59%) with a normal response, in whom HC was discontinued. In these 13 patients, the median peak cortisol level to postoperative CRH stimulation was 480 (340–543) nmol/L, whereas the median peak cortisol level during the second test were 672 (570–890) nmol/L ($P < 0.001$). The clinical characteristics of these patients are detailed in Table 2. Based on the results of the CRH test, four patients did not receive HC directly after surgery, or only if necessary. In two of these patients (Table 3; patient 2 and 8) the physician defined the HPA axis as normal based on the peak cortisol of the CRH test (540 and 543 nmol/L respectively). No clinical events were reported.

In 20 of these 42 patients with a median CRH-stimulated cortisol concentration of 194 (6–510) nmol/L, no additional stimulation test of adrenal function was performed during follow-up, but basal morning cortisol levels after the withdrawal of hydrocortisone for 18-24 h were used to assess the axis. Persistent adrenal insufficiency was considered to be present in these 20 patients because of pre-existent panhypopituitarism before or immediately after surgery (n=12), pre-existent isolated severe adrenal insufficiency before surgery (n=4) or very low basal serum cortisol concentrations (mean 10 nmol/L) during follow-up after surgery (n=4). Accordingly, all these patients received hydrocortisone supplementation directly after the post surgical CRH test until now.

Patients with a normal postoperative cortisol response to CRH (n=102)

The peak levels of cortisol during the postoperative CRH test classified 102 of the 144 patients with normal pituitary-adrenal function (peak cortisol > 550 nmol/L) (Figure 1). In 75 of these 102 patients, adrenal

function was assessed during follow-up using a second stimulation test and by basal postabsorptive cortisol levels only in the other 27 patients. These 27 patients were not subjected to a second stimulation test because of basal serum cortisol levels > 550 nmol/L (n=12), normal urine cortisol levels (n=3), short follow-up between repeated surgery or additional radiotherapy (n=2), and follow-up < 1 yr (n=2) or unspecified reasons (n=7). One patient returned within three months after surgery with complaints and basal postabsorptive serum cortisol levels of 90 nmol/L and HC was started without additional stimulation test. The ITT was used in 49 of the 75 patients, the CRH test in 11 patients, the ACTH stimulation test in 11, and the metyrapone test in four patients. A normal response to these tests was found in 62 patients. However, 13 patients had an insufficient adrenal response to these tests. With the inclusion of the patient with very low basal serum cortisol levels (see above), 14 patients were classified as adrenal insufficient (Table 3). Thirteen of these 14 patients had been diagnosed with any other additional pituitary insufficiencies and 8 of these patients (57%) had panhypopituitarism. Six patients already received HC directly after surgery. None of these 14 patients experienced any clinical event related to cortisol deficiency.

Prevalence of additional pituitary insufficiency

A total of 73 patients had additional pituitary insufficiency. The prevalence of additional pituitary insufficiency was significantly higher in patients diagnosed with an insufficient CRH stimulation test after surgery compared to patients with a normal test result (any hypopituitarism $P < 0.001$; GHD $P < 0.001$; TSH deficiency $P < 0.001$; LH/FSH deficiency $P = 0.001$).

Table 2. Patients incorrectly diagnosed with adrenal insufficiency based on the CRH test directly after surgery

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
1	M	53	NFA	410	y	3 mnths	ACTH	890	LH/FSH, GHD	No optimal reaction CRH test, HC discontinued before confirmation test. After 3 years ITT peak cortisol 860 nmol/L	n
2	M	48	Acromegaly	540	n	3.8	CRH	790	None	After CRH test HPA axis defined as normal, no HC	n
3	M	23	Acromegaly	480	n	4.9	ITT	780	None	After CRH test another CRH test and 24h urine still not sufficient.; ITT after 4 years insufficient	n
4	F	26	Prolactinoma	480	y	8.9	ITT	750	DI	HC until next outpatient appointment; 5 yrs loss to follow-up; recurrence of prolactinoma treatment with Dostinex. Did not use HC. 8 yrs after surgery 2 sufficient ACTH tests and 1 yr later normal ITT	n
5	M	53	NFA	440	y	1 mnth	CRH	710	GHD	HC discontinued after CRH test. (9 yrs after surgery RT)	n
6	F	62	NFA	469	y	7 mnths	ITT	696	GHD	After 4 months ACTH peak cortisol 580 therefore stop HC. 3 months later ITT	n

Table 2. Continued

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
7	M	59	NFA	457	y	7 mnths	ACTH	672	TSH, LH/FSH, GHD	HC discontinued; after 5 months ACTH test insufficient peak cortisol 445 nmol/L. Followed by 3 more ACTH tests (7–9months after surgery) all normal cortisol response. ITT 1 yr after surgery however nadir 2.3 mmol/L; cortisol peak 574 nmol/L.	n
8	F	72	Acromegaly	543	n	1.2	CRH	665	None	HPA axis defined as normal, no HC	n
9	F	56	NFA	520	y	3.9	ITT	657	Panhypopit	After 6 months ACTH test normal; 1 month later ITT peak cortisol 550 nmol; HC lowered to 10 mg/day. 10 months later ITT normal response cortisol; stop HC. 2 yrs later another ITT	n
10	M	38	Acromegaly	340	y	10.3	ITT	634	None	Received HC before surgery, discontinued after surgery followed by CRH test after 3 months; peak cortisol 560 nmol/L. 10 yrs after surgery ACTH test followed by ITT both normal cortisol responses.	n

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
11	M	42	Acromegaly	530	i.n.	11.6	ACTH	618	None	Based on CRH only HC if necessary. Shortly after CRH test ACTH test with normal cortisol response; no HC necessary. 11 yrs later another ACTH test	n
12	F	42	NFA	482	y	1.3	CRH	606	None	6 months after surgery 1st ACTH test; insufficient cortisol response; followed by 4 ACTH tests within 6 months. All insufficient cortisol response. Followed by a CRH tests with a sufficient response.	n
13	F	39	Acromegaly	500	y	4.1	ITT	570	None	4 months after surgery 2nd CRH test still insufficient cortisol response; continue HC. 1 yr later ITT; peak cortisol 520 nmol/L. 3 yrs later 2nd ITT sufficient stop HC	n

M, male; F, female; NFA, non functioning adenoma; n, no; y, yes; i.n., if necessary; DI, diabetes insipidus; ITT, insulin tolerance test; CRH, corticotropin releasing hormone; HC, hydrocortisone; GHD, growth hormone deficiency.

Table 3. Patients who appeared to be adrenal insufficient based on a second test or basal serum cortisol concentration during follow-up

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
1	M	55	NFA	750	n	2 months	ITT	512	Panhypopit	Before surgery panhypopituitarism; ITT after 2 months insufficiënt	n
2	M	50	NFA	690	n	1.7	ITT	510	Panhypopit	Not all results known when patient left hospital. Appeared to be TSH- and GH deficient. Outpatient follow-up 1st ITT sufficient; 2nd ITT insufficient	n
3	M	19	NFA	780	n	6.5	ITT	480	Panhypopit	After surgery gonadotrophic deficiency; ITT 2002 sufficient; ITT insufficiënt; corticotrope and GH deficiency; start suppletion	n
4	F	50	NFA	640	y	1.8	ITT	410	Panhypopit	After surgery HC ; follow-up after 1 year Metyrapone test insufficient; 1 yr later ITT still insufficient	n
5	F	53	NFA	1100	y	2 months	Metyrapone test	90	TSH, GHD	Before surgery TSH deficiency and hypocortisolism; Start HC after surgery; 2 mnths after surgery ACTH and Metyrapone test both insufficient	n
6	M	60	NFA	600	y	6 months	ITT	200	Panhypopit	Received HC before surgery; continued after surgery; follow-up after 6 months	n

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
7	F	57	NFA	670	n	3.4	Metyrapone test	190 159	Panhypopit	1 yr after surgery new CRH test sufficient. Complaints of tiredness. 2 yrs later Metyrapone insufficiënt.	n
8	M	54	NFA	670	n	4.3	ACTH 1 ug	170	Panhypopit	After surgery gonadotropic and GH deficiency. After 3 yrs start rhGH; 2 yrs later low cortisol 24h urine and hypothyroidism. Euthyreotic state ACTH test insufficiënt start HC	n
9	F	78	NFA	620	n	3 months	Metyrapone test	120 84.9	None	Cardial problems; follow-up in outpatient clinic	n
10	F	77	NFA	610	y	2 days	Metyrapone test	90 79.5	TSH, DI	Based on low basal serum cortisol levels start HC; 2 days after CRH metyrapone test insufficient.	n
11	F	50	NFA	770	n	7	Metyrapone test	90 107	Gonadotrope, GHD	Several years no complaints no insufficiency; 2002 ITT GHD followed by therapy; 2004 metyrapone insufficient	n

Table 3. Continued

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
12	F	67	NFA	600	y	1.4	ITT	4	Panhypopit	Directly post surgery probably panhypopit because of lesion/rupture pituitary stalk. No basal ACTH production with stimulation after CRH; Start HC	n
13	M	38	NFA	797	n	3 months	Basal serum cortisol	90	Panhypopit	Before surgery panhypopit; CRH test normal. 3 months after surgery complaints with low basal serum cortisol. Start HC	n
14	M	39	NFA	660	y	5 months	ACTH-test	300	GHD, gonadotrope, DI	Before surgery panhypopituitarism. Probably HC during CRH test after surgery.	n

M, male; F, female; NFA, non functioning adenoma; n, no; y, yes; DI, diabetes insipidus; ITT, insulin tolerance test; CRH, corticotropin releasing hormone; HC, hydrocortisone; GHD, growth hormone deficiency.

Discussion

This study evaluated the postoperative response of cortisol to CRH stimulation in a large cohort of patients after TS for pituitary adenomas compared with the adrenal function assessed during postoperative follow-up. The second adrenal function test documented a normal cortisol response in 31% of the patients with a decreased cortisol response to CRH stimulation directly after surgery. Conversely, the second adrenal stimulation test documented an insufficient cortisol response in 14% of the patients with a normal cortisol response to direct postoperative CRH stimulation. Therefore, the postoperative CRH test does not reliably predict adrenal function after TS for pituitary adenomas in all patients. Nonetheless, our substitution strategy of hydrocortisone guided by the postoperative cortisol responses to CRH did not result in any case of adrenal crises in our patients.

Although CRH stimulation has been incorporated in the diagnostic procedures of ACTH dependent Cushing's syndrome (21–23), reports on the use of CRH stimulation to assess cortisol dependency after transsphenoidal surgery for other pituitary adenomas are scarce. We found three publications that assessed pituitary function using CRH, but these were not specifically in patients after transsphenoidal surgery (8;9). Dullaart *et al.* (9) and Schmidt *et al.* (8) compared the CRH test with basal serum cortisol levels and found no higher diagnostic applicability of the CRH test to basal morning cortisol levels. In contrast, Maghnie *et al.* concluded that the CRH test provided better results than the short Synacthen test (SST) and low-dose short Synacthen test (LDSST), and that CRH may be useful in patients who have a contraindication for ITT (6).

In the current study, the postoperative CRH stimulation test classified 42 of the 144 patients with hypocortisolism. However, 13 of these patients had sufficient adrenal function during follow-up. There are several explanations for these discrepant results. They may be related to differences in cut-off values of the different tests. Regularly accepted

cut-off values (500-550 nmol/L) have been defined for the ITT, which still remains the gold standard test for the assessment of the HPA axis. For the CRH test, some authors have proposed different cut-off values for peak cortisol responses. For example, Schmidt *et al.*(8) reported an optimal peak cortisol cut-off of < 377 nmol/L, yielding a 96% specificity, but poor sensitivity of 76% for the diagnosis of adrenal insufficiency (8). A sensitivity of 100% was reached using a peak cortisol levels of 514 nmol/L (with a specificity of 32%), and 100% specificity with peak cortisol levels of 349 nmol/L (sensitivity 66%). Dullaart *et al.* found that a peak cortisol value of 420 nmol/L reflected 100% specificity, but 100% sensitivity for the CRH test was only reached using a peak cortisol of 615 nmol/L. Because in our center the CRH test is used as a screening test for hypocortisolism after TS to identify those patients that require hydrocortisone supplementation, we applied a generally accepted stringent criterion of 550 nmol/L. The data indicate that this choice for a higher sensitivity of the CRH test is at the expense of a lower specificity. In other words, using this strategy a higher proportion of patients will be incorrectly diagnosed with adrenal insufficiency. Based on the available literature the use of a cut-off levels of peak cortisol of 514 nmol/L would have resulted in 4/13 patients which would not have been diagnosed with adrenal insufficiency, but with the criteria suggested by Dullaart *et al.* even more patients would have had discrepant results (8;9).

Recovery of preoperative adrenal insufficiency following TS has been described previously (24;25). In a recent study that compared the ITT response at 3 and 12 months after TS, recovery of adrenal function was demonstrated within the first year (26). In agreement, we found a normal function of the HPA axis in eight patients within the first year after surgery who were initially diagnosed as being adrenal insufficient, indicating the necessity of an extensive follow-up in patients after surgery within one year.

In the current study, the postoperative CRH test classified 102 of the 144 patients as having a normal functioning of the HPA axis based on the post-operative CRH test. Fourteen percent of these patients later proved to have hypocortisolism by a second test. These discrepant test results can be potentially life-threatening because these patients are at risk for adrenal crises. It is possible that additional pituitary insufficiencies affected pituitary-adrenal function. Growth hormone and thyroid hormone deficiency can influence these test results. Growth hormone replacement

therapy in patients with GH deficiency 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 interconversion (27) . The use of GH replacement therapy in GH deficient patients may therefore unmask cortisol deficiency (28;29). This may also be the case in some of our patients, because their adrenal insufficiency became clear after start of rhGH therapy. Despite all the confounding factors none of our patients had a clinical event.

In conclusion, the CRH test can be safely used to guide hydrocortisone substitution after TS. Nonetheless, the cortisol response to this test cannot 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 (see Figure 2). This approach is not required in patients with an impaired postoperative cortisol response to CRH, who have multiple pituitary insufficiencies.

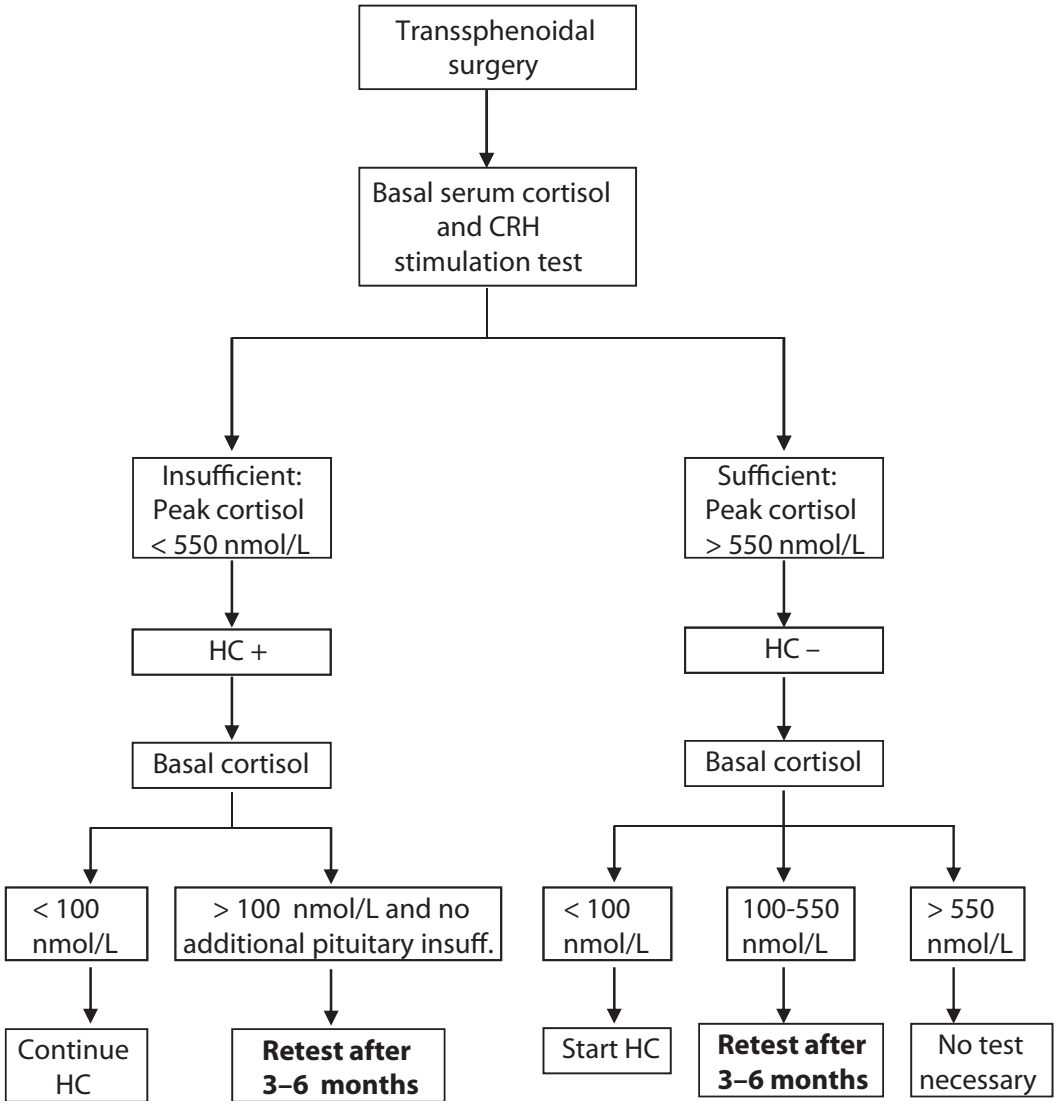

Figure 2. Proposed algorithm for the postoperative follow-up of adrenal function in non ACTH dependent pituitary disease (HC; hydrocortisone)

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Chapter 5

Low incidence of adrenal insufficiency after transsphenoidal surgery in patients with acromegaly: a long-term follow-up study

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Equal contribution

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Abstract

Context: The long-term prevalence of adrenal insufficiency after transsphenoidal surgery for GH secreting pituitary adenomas is unknown. However, recently a single study reported a high prevalence of adrenal insufficiency in acromegalic patients after surgical and/or medical treatment without postoperative radiotherapy.

Objective: The objective of the study was to assess the prevalence and incidence rates of adrenal insufficiency in consecutive patients during long-term follow-up after successful transsphenoidal surgery for acromegaly.

Design: In 91 consecutive patients in remission after transsphenoidal surgery only, we retrospectively reviewed insulin tolerance tests, CRH stimulation tests, metyrapone tests, and ACTH stimulation tests used to assess corticotrope function.

Results: Early postoperatively, insufficient adrenal function was observed in 16 patients (18%), which was transient in eight and irreversible in eight other patients in the first year of postoperative follow-up. Therefore, after the first year, the prevalence of adrenal insufficiency was 9%. Late, new-onset adrenal insufficiency developed in only three patients 13, 18, and 24 yr after surgery. The incidence rate of late adrenal insufficiency after successful surgery was 2/1000 person-years. After long-term follow-up, a median of 8.1 (1–31 yr), the prevalence of secondary adrenal insufficiency was 12% in patients in remission after surgery for acromegaly.

Conclusion: The prevalence of adrenal insufficiency 1 yr after surgery was 9%, whereas during prolonged follow-up, the incidence rate of adrenal insufficiency was only 2/1000 person-years in patients in 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.

Introduction

Acromegaly is a chronic disabling disease caused by a GH-producing pituitary adenoma. Transsphenoidal surgery is the curative treatment of choice and somatostatin analogs or radiotherapy is given as needed (1). Hypopituitarism, requiring replacement therapy, can be present postoperatively as a result of surgical or additional radiotherapy. Pituitary irradiation induces hypopituitarism in 50%–75% of the patients after 10–20 yr of follow-up (2). The prevalence of late-onset hypopituitarism in surgically treated patients is not precisely known, but it is generally considered to occur infrequently. The 2009 guidelines on management of acromegaly state that pituitary function should be assessed three months after surgery and that if a dynamic evaluation reveals normal function, there is no need for repeated dynamic function tests unless a patient receives radiotherapy or has clinical symptoms of hypopituitarism (1). Recently, however, Ronchi *et al.* (3) evaluated adrenal function using the low-dose 1 μg ACTH stimulation test in 36 patients with acromegaly treated by surgery with or without somatostatin analog treatment or by primary medical treatment with somatostatin analogs. A cut-off value for cortisol of 500 nmol/L was used to demonstrate normal adrenal function. They reported a high prevalence of adrenal insufficiency in 32% of patients after a median duration of follow-up of 6 yr after surgery and eventually somatostatin analog treatment. The authors concluded that hypothalamic-pituitary-adrenal (HPA) axis function 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 nonirradiated patients with acromegaly (3). However, the high prevalence of HPA axis insufficiency in surgically treated acromegalic patients is not yet confirmed by others. Therefore, the aim of the present study was to evaluate the prevalence of adrenal insufficiency during long-term follow-up in an unselected cohort of consecutive patients in remission of GH excess by transsphenoidal surgery in our hospital during the period of 1979–2003.

Patients and Methods

Patients

For this study, all 164 consecutive patients, diagnosed with acromegaly and treated at the Leiden University Medical Center, a tertiary referral center, by transsphenoidal surgery between 1979 and 2003 were reviewed. For the purpose of this study, we excluded patients, who were additionally treated by radiotherapy (n=59) as well as patients who had persistent active disease after surgery (n=14). Consequently, 91 patients were included. The diagnosis of acromegaly was based on clinical characteristics and confirmed by insufficient suppression of GH levels after an oral glucose tolerance test. All patients had careful preoperative and postoperative biochemical evaluation. Criteria for cure were serum GH less than 2.5 μg/L, normal glucose-suppressed GH levels (<1.25 μg/L for the RIA and <0.38 μg/L for the immunofluorometric assay), and normal IGF-I values for age. During postoperative follow-up, serum GH, glucose-suppressed GH levels, and IGF-I values were measured at yearly intervals. The surgical results of the complete cohort have been reported previously (4). Data regarding clinical and biochemical characteristics, treatment, and pituitary function were available from all patients. HPA axis function was routinely studied early postoperatively (7–10 days postoperatively), using the CRH test or the insulin tolerance test (ITT). Thereafter nonstimulated morning cortisol measurements were performed at yearly follow-up visits, and dynamic tests to assess corticotrope function were performed at increasing nonstandardized follow-up intervals. The Medical Ethical Committee approved the analysis of treatment results in patients with acromegaly, and no informed consent was required for this retrospective analysis.

Methods

We retrospectively evaluated HPA axis function in the total, unselected cohort of patients in remission after surgery to exclude a potential selection bias. None of the patients received pharmacological treatment

for acromegaly. We reviewed all available dynamic tests in our database performed to evaluate corticotrope function. We considered the ITT as the gold standard test. If ITT results were not available, other stimulation tests like the CRH, ACTH, and metyrapone tests were evaluated. In addition, basal morning cortisol values were collected. Patients were considered to have adrenal insufficiency if they had biochemically confirmed insufficiency (see below). All patients had an endocrine assessment every year. The use of hormone stimulation tests changed during the follow-up period. Initially, ITT was used early postoperatively and during follow-up. After the clinical introduction of the CRH and GHRH test, the ITT lost its leading position in the screening for somatotrope and corticotrope deficiencies for obvious reasons. From 1990 onward, according to protocol, the CRH test was performed early postoperatively to assess whether corticotrope function was sufficient to discharge patients without hydrocortisone replacement, and confirmation tests were performed at the outpatient department.

The metyrapone test was used for follow-up assessment in patients with contraindication for ITT. In recent years, 1 μg ACTH tests were performed to screen for corticotrope deficiency in late follow-up. However, the ITT remained the gold standard for confirmation of adrenal insufficiency, especially if other test revealed borderline results (in patients without a contraindication for ITT).

Evaluation of HPA axis

An insulin tolerance test (insulin 0.1 IE/kg, Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was administered i.v. in the postabsorptive state between 0800 and 0900 h to induce hypoglycemia (< 2.2 mmol/L). Cortisol was measured at -15, 0, 15, 30, 45, 60, 90, and 120 min. A cut-off value of cortisol greater than 550 nmol/L was used to define normal function of the HPA axis (5–9). An ACTH stimulation test (ACTH 1μg Synacthen®; Novartis Pharma B.V., Arnhem, The Netherlands) was administered i.v. between 0800 and 0900 h after blood samples had been taken at -15 and 0 min for measurement of cortisol values. The response of cortisol to ACTH was assessed in a single blood sample obtained 30 min after ACTH injection. A cut-off value of cortisol greater than 550 nmol/L was used to define normal adrenal function (10–12).

CRH test (CRH 100 μg; Ferring B.V., Hoofddorp, The Netherlands) was administered in the postabsorptive state between 0800 and 0900 h.

Cortisol and ACTH were measured at -15, -5, 15, 30, 45, and 60 min. A cut-off value for cortisol of greater than 550 nmol/Liter was used to define normal function (13, 14). A Metyrapone test (metyrapone 30 mg/kg, Metopiron; Novartis Pharma B.V., Arnhem, The Netherlands) was administered at midnight. The next morning postabsorptive blood samples were obtained for measurement of 11-deoxycortisol, cortisol, and ACTH levels. A cut-off value for 11-deoxycortisol of 200 nmol/L was used to define normal adrenal function (15–17).

For morning cortisol, blood was sampled between 0800 and 0900 h for assessment of cortisol values. A cut-off value of cortisol greater than 500 nmol/L was used to define normal function only in case dynamic tests were not available. Premenopausal women were tested after stopping estrogen replacement for 3 months.

Assays

Cortisol was measured between 1978 and 1986 by in-house RIA with an interassay coefficient of variation (CV) of 10% and with a detection limit of 5 nmol/L. Between 1986 and 1994, cortisol was measured by fluorescence energy-transfer immunoassay (Syva-Advance; Syva Co., Palo Alto, CA) with an interassay variation coefficient of 3.6–6.1% and a detection limit of 0.05 μmol/L. From 1994, cortisol was measured by fluorescence polarization assay on a TDx (Abbott Laboratories, Abbott Park, IL). The interassay variation coefficient is 5–6% above 0.50 μmol/L and amounts to 12% under 20 nmol/L. The detection limit was 2 nmol/L. Before 1993 GH was measured by RIA (Biolab; Serona, Coissins, Switzerland), calibrated against World Health Organization international reference preparation 66/21 (detection limit: 0.5 mU/L, with an interassay CV less than 5%; for the conversion of micrograms per liter to milliunits per liter, multiply by 2). After 1993 serum GH concentration was measured with a sensitive time-resolved fluoroimmunoassay (Wallac, Turku, Finland). The assay is specific for 22 kDa GH. The standard was recombinant human GH (Genotropin; Pharmacia & Upjohn, Uppsala, Sweden), which was calibrated against the World Health Organization First International Reference Preparation 80/505 (to convert milliunits per liter to micrograms per liter, divide by 2.6) (18). The limit of detection (defined as the value 2 SD above the mean value of the zero standard) was 0.03 mU/L (0.0115 μg/L). The intraassay CV varied from 1.6 to 8.4% in the assay range 0.26–47 mU/L, with corresponding interassay CV of

2.0–9.9%. Until 2005 serum IGF-I concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/L and an interassay CV below 11%. IGF-I is expressed as SD scores for age- and gender-related normal levels determined in the same laboratory (18). From 2005 onward, serum IGF-I concentration (nanograms per milliliter) was measured with an immunometric technique on the Immulite 2500 system (Diagnostic Products Corp., Los Angeles, CA). The intraassay CV was 5.0 and 7.5% at mean serum concentrations of 8 and 75 nmol/L, respectively. The IGF-I concentration was expressed as SD score, using the λ-μ-σ smoothed reference curves based on measurements in 906 healthy individuals (19).

Statistical analysis

All results are shown as mean±SD. Descriptive statistics were calculated. Student's t-tests were used when appropriate. $P < 0.05$ was considered to be statistically significant. Duration of follow-up in person-years was calculated for all patients as time between surgery until July 1, 2010, if patients were followed-up in our center, until date of secondary treatment in case of a recurrence, until last visit if patients were lost to follow-up, or until date of death in case patients had died. Incidence rates were calculated using number of cases divided over person-years of follow-up. Analyses were performed by SPSS package (version 16.0.2, 2008; SPSS, Chicago, IL).

Results

Baseline characteristics

We included 91 consecutive patients, 49 male and 42 female patients cured by transsphenoidal adenomectomy for a GH producing pituitary adenoma (Table 1). The mean age at the time of surgery was 46.8 ± 12.3 yr (range 18–76 yr). The mean disease duration before surgery was 9.0 ± 8.0 yr. Twenty-eight patients had a microadenoma (31%), 55 had a noninvasive macroadenoma (60%), and eight had an invasive macroadenoma (9%). Mean GH preoperative concentrations and IGF-I SD scores decreased significantly after surgery ($P < 0.001$, Table 1). Mean GH concentrations were 0.8 ± 1.0 μg/L, and IGF-I SD scores were 0.8 ± 2.1 at the end of follow-up.

Immediate postoperative assessment of adrenal function

Seven to 10 days after surgery, assessment of adrenal function was performed by CRH test (49%), ITT (43%), or by basal cortisol level in a minority of patients (2%). Three patients (3%) were not retested postoperatively because they had been cortisol dependent preoperatively. Data were missing in 2%. Sufficient adrenal function was observed in 36 of 44 patients according to the results of the CRH test, 35 of 39 patients according to ITT, and one of two patients according to basal cortisol. Thus, early postoperative adrenal insufficiency was observed in 16 patients (18%) including the three patients with preoperative secondary insufficiency. Hydrocortisone replacement was prescribed to 11 patients.

Table 1. Baseline characteristics and follow-up characteristics of patients with acromegaly cured by transsphenoidal surgery

	Patients (n=91)
M/F	49/42
Age at TNS (yrs)	46.8 ± 12.3 (range: 18–76)
Disease duration (yrs)	9.0 ± 8.0
Tumorclass (n(%))	
Class 1 – Microadenoma	28 (31%)
Class 2 – Non-invasive macroadenoma	55 (60%)
Class 3 – Invasive macroadenoma	8 (9%)
Preoperative GH (µg/L)	23.1 ± 27.1
Postoperative GH (µg/L)	0.9 ± 0.8
Follow-up GH (µg/L)	0.8 ± 1.0
Preoperative IGF-I SD	7.4 ± 4.2
Postoperative IGF-I SD	0.9 ± 1.9
Follow-up IGF-I SD	0.8 ± 2.1
Follow-up	
Pituitary deficiencies	
TSH	8 (9%)
LH/FSH	11 (12%)
GH	8 (14%)*

F, female; M, male; TNS, transnasosphenoidal surgery

Data are shown as mean ± SD unless mentioned otherwise. Significant decrease following surgery (P <0.001) for both GH and IGF-I SD. No difference between postoperative and follow-up concentations (P=ns). *Assessed in 58 patients by ITT.

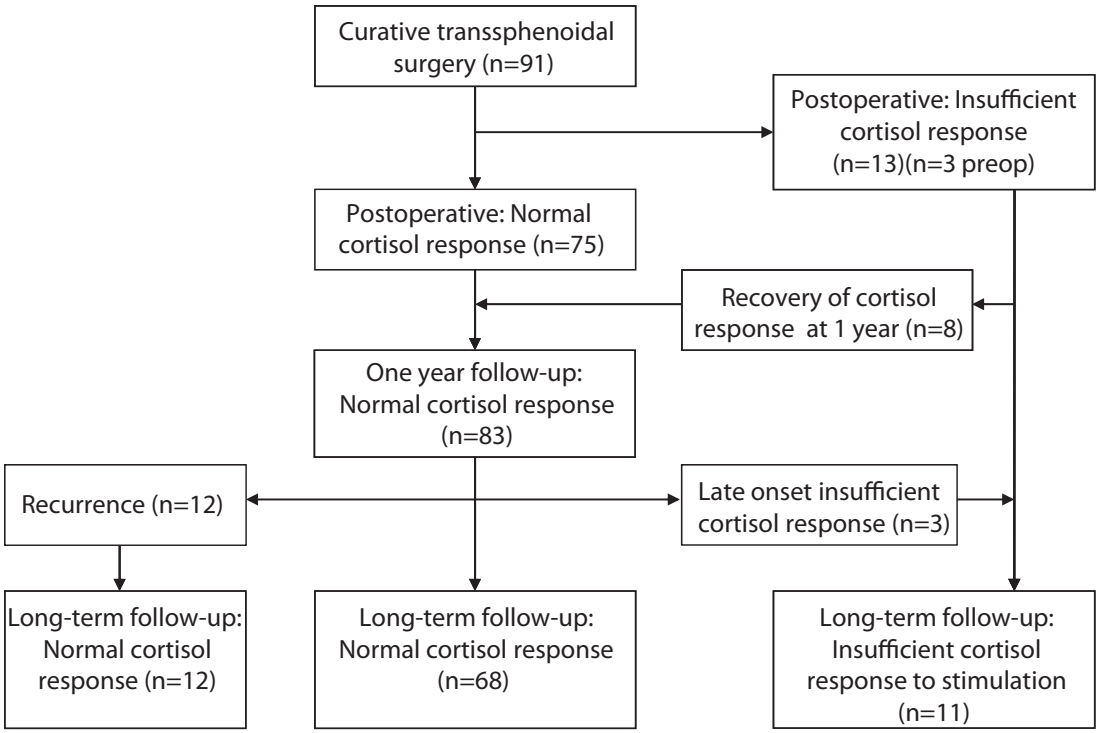

Figure 1. Flowchart of corticotrope function during long-term follow-up

Adrenal function 1 yr after surgery

At 1 yr postoperatively, the prevalence of adrenal insufficiency was 9% (eight of 91), three patients being diagnosed preoperatively and five patients diagnosed early postoperatively. These eight patients received hydrocortisone replacement therapy. Adrenal insufficiency was diagnosed by insufficient response to ITT (n=3), CRH (n=3), metyrapone test (n=1), or low basal cortisol of 20 nmol/L (n=1).

In the eight other patients with an early postoperative insufficient cortisol response to dynamic testing (CRH or ITT), retesting within the first year revealed normal adrenal function. The results of postoperative tests and follow-up tests in these patients are detailed in Table 2.

Adrenal function during prolonged follow-up

During prolonged follow-up, 262 ITT, 110 CRH tests, and 67 ACTH tests were performed in the patients cured by transsphenoidal surgery. Twelve patients with initial cure developed a recurrence of acromegaly (13%) a median of 8.7 yr (range 1.2–24.6 yr) after surgery. Consequently, 79 patients were in long-term cure after surgery only. Patients with

a recurrence of acromegaly were followed up until the date of the secondary treatment for the present analysis. At late evaluation (n=91), a median of 8.1 yr (1–31 yr) postoperatively, corticotrope function was assessed by ITT (67%), CRH (7%), ACTH (10%), or basal cortisol levels greater than 0.50 μmol/Liter (6%), whereas there were no data available in 10% of patients due to death (n=3) or loss to follow-up (n=6). During long-term follow-up of 1489 person-years, lateonset adrenal insufficiency developed in three patients (3%) 13, 18, and 24 yr postoperatively. The incidence rate for new-onset adrenal insufficiency was 2/1000 person-years. The clinical characteristics of these patients with late-onset adrenal insufficiency and their presenting symptoms of late adrenal deficiency are detailed in Table 3. All three patients had been treated for a noninvasive macroadenoma. Two patients had complaints of tiredness, dizziness, and/or general malaise. The third patient presented with unexplained hypoglycemias. Due to high age, no ITT was performed, but the ACTH test revealed insufficient response of cortisol. All patients improved clinically after replacement therapy. Thus, at the end of follow-up, adrenal insufficiency was present in 12% (11 of 91) of the patients in remission after transsphenoidal surgery. All these patients required hydrocortisone replacement therapy.

Table 2. Biochemical and clinical characteristics of patients with insufficient early postoperative adrenal function test, but recovery of adrenal function at repeat testing

Gender	Age at TSS (yr)	Postoperative test	Basal cortisol (µmol/L)	Peak cortisol (µmol/L)	Postoperative follow-up*	Follow-up test	Basal cortisol (µmol/L)	Peak cortisol (µmol/L)
M	38	CRH	0.26	0.34	Temporary hydrocortisone replacement	CRH	0.27	0.56
F	47	ITT	0.16	0.42	No Hydrocortisone replacement. Test and basal cortisol considered adequate.	basal cortisol	0.82	
M	46	ITT	0.13	0.47	No Hydrocortisone replacement	ITT	0.36	0.64
M	23	CRH	0.32	0.48	No Hydrocortisone replacement	ITT	0.28	0.78
M	23	CRH	0.34	0.48	No Hydrocortisone replacement	ITT	0.17	0.58
F	39	ITT	0.30	0.50	Temporary hydrocortisone replacement	ITT	0.15	0.57
M	52	CRH	0.37	0.52	Temporary hydrocortisone replacement	ITT	0.25	0.71
M	42	CRH	0.43	0.53	Hydrocortisone if needed.	ACTH	0.42	0.62

ACTH, adrenocorticotrope hormone; CRH, corticotrope releasing hormone; F, female; HC, hydrocortisone; ITT, insulin tolerance test; M, male; TSS, transsphenoidal surgery

*Postoperative management was decided by own physician.

Table 3. Characteristics of patients cured for acromegaly with late onset adrenocortical insufficiency

Gender	Age at TSS (yr)	Tumorclass*	Postoperative test	Basal Cortisol (µmol/L)	Peak cortisol (µmol/L)	Clinical follow-up	Test diagnose		Start HC after (yr)	Other pituitary deficiencies
							Stimulation test	*Results*		
M	33	2	ITT	0.09	0.55	Tiredness, malaise, chest pain, paresthesias	Metyrapone	11-DOC 44.3 cort 0.13	24	None
F	43	2	ITT	0.42	0.62	Headache, tiredness, astenia Yearly follow-up: basal cortisol 0.02 nmol/L	#		13	GH-TSH
F	67	2	ITT	0.34	0.60	DM II Unexplained hypoglycemia	ACTH –test**	Basal cort 0.16 Peak cort 0.47	18	GH-LH/FSH

ACTH, adrenocorticotrope hormone; cort, cortisol (µmol/L); CRH, corticotrope releasing hormone; DM, diabetes mellitus; 11-DOC, 11-deoxycortisol (nmol/L); F, female; FSH, follicle stimulating hormone; GH, growth hormone; HC, hydrocortisone; ITT, insulin tolerance test; LH, luteinizing hormone; M, male; TSS, transsphenoidal surgery; TSH, thyroid stimulating hormone

* Tumorclass 2 – non-invasive macroadenoma

#Based on low basal serum cortisol no stimulation test was performed.

** Due to high age at, no ITT was performed to confirm adrenal insufficiency

Discussion

The present study documents that new-onset adrenal insufficiency after successful surgical treatment for acromegaly in follow-up is not frequently observed. The prevalence of adrenal insufficiency was 9% 1 yr after surgery. In our well-characterized cohort of consecutive patients in remission after transsphenoidal surgery, the incidence rate of new-onset late adrenal insufficiency was only 2/1000 person-years during a long-term clinical follow-up. In accordance with the study by Ronchi *et al.* (3), our study demonstrates that HPA axis function may worsen over time, but adrenal insufficiency is an infrequent complication in patients in remission of acromegaly after surgery.

The discrepancies in the prevalence of adrenal insufficiency between the current study and the study by Ronchi *et al.* (3) may be explained by differences in study design and study population. In the study by Ronchi *et al.*, 16 of 36 patients had neuroradiological evidence of residual postoperative tumor remnants, and 16 were treated by somatostatin analogs. In addition, the authors used the low-dose ACTH stimulation test, which may lead to a false-negative response in 10% of healthy subjects (20).

Furthermore, Ronchi *et al.* used a cut-off value for cortisol of 500 nmol/L for the evaluation of the HPA axis, whereas we used mainly the ITT and CRH test with a cut-off value of 550 nmol/L. The ITT is generally regarded as the gold standard (7;21). Alternatively, the differences between the two studies may also be caused by patient selection and differences in surgical techniques. Ronchi *et al.* (3) observed a remarkably high prevalence of adrenal insufficiency in 32% of the patients treated by surgery and/or somatostatin analogs for acromegaly. However, only 16% of their patients required substitution therapy with hydrocortisone, in agreement with our data.

Potential caveats in our study include changed cortisol binding globulin (CBG) levels in acromegaly and the presence of postoperative GH deficiency. However, studies on the effect of GH on serum CBG

concentration are controversial. Some authors reported that GH administration in hypopituitary patients decrease CBG levels by approximately 20% (22–24), but other studies in larger cohorts did not observe a difference in CBG levels during GH treatment (25;26). Data on CBG concentrations in patients with active acromegaly are also scarce. One study investigated the effect of pegvisomant treatment on cortisol metabolism (27). These authors did not observe any change in serum CBG concentrations, although the majority of the patients reached normal IGF-I levels. Collectively these data indicate that the effect of GH on serum CBG levels is not unequivocal, especially in GH-deficient patients, and an increase in CBG concentrations after GH normalization in acromegaly has not been demonstrated.

GH has a strong impact on cortisol metabolism by its action on 11β-hydroxysteroid dehydrogenase, leading to increased cortisol-cortisone interconversion (28). For instance, GH replacement therapy in GH-deficient patients may unmask cortisol deficiency (23;26). In our study, untreated GH deficiency in the presence of a normal corticotrope function was present in only three of 58 patients (5%) with available GH measurements during ITT (data not shown), suggesting that it is unlikely that this significantly affected our results. Patients underwent surgery on a low-dose dexamethasone scheme, which may have influenced the test results, leading to overestimation of adrenal insufficiency shortly after surgery. Indeed, in eight patients with suboptimal cortisol response to ITT or CRH postoperatively, adrenal function normalized within 1 yr. This observation is in accordance with a recent study that compared the ITT response at 3 and 12 months postoperatively (29). In that study, cortisol peak responses increased by 17% and adrenal function had recovered in four of 20 patients with an insufficient cortisol peak response directly after surgery.

Recovery of preoperative adrenal insufficiency after transsphenoidal surgery has been described previously (30;31). Therefore, early postoperative testing may not reflect the definitive outcome of adrenal function. The outcome of these tests can be influenced by incipient GH or thyroid hormone deficiency, as discussed above (32). This observation emphasizes the importance of repeated dynamic tests also in patients with early postoperative insufficient response to adrenal function tests. After 1 yr, less frequent control of dynamic pituitary function may suffice in those patients with a confirmed normal adrenal function.

A recent meta analysis of 12 studies on the diagnostic value of basal cortisol values using summary receiver-operating characteristic curves showed an area under the curve of 0.79 (95% confidence interval 0.75–0.82). A lower cut-off value for basal cortisol less than 140 nmol/L (likelihood ratio > 9) was used to diagnose hypoadrenalism and an upper cut-off value of greater than 370 nmol/L (likelihood ratio < 0.15) was used to exclude hypoadrenalism. To be eligible for inclusion in this study, adult and pediatric subjects had to be suspected of adrenal insufficiency from pituitary disease longer than four wk from prolonged exogenous glucocorticoid administration. Only studies with ITT or metyrapone test as a reference test were included (33). It seems reasonable to use the guidelines as proposed by these authors. Thus, in patients with a basal serum cortisol greater than 370 nmol/L without complaints, the likelihood to have adrenal insufficiency is very low, and screening using basal cortisol may suffice in asymptomatic patients.

We had the opportunity to review long-term follow-up data in a carefully followed cohort and to have the availability of multiple tests in the vast majority of patients in the presence of few missing data. Nonetheless, limitations of our study are the retrospective nature of the study and the fact that patients had been tested using different cortisol stimulation tests and assays. However, this does not affect our conclusions because 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. Nevertheless, several reports suggest that the sensitivity of the CRH test is less than that of the ITT (34–38). This conclusion is partly related to the cut-off value of CRH-stimulated cortisol responses. Unfortunately, there are no large studies of the CRH test in healthy subjects across ages, body mass index, and gender.

Therefore, we used a restrictive approach and retested subjects with an insufficient response to CRH by ITT. The CRH test may not detect hypothalamic insufficiency, whereas the ITT is a test for the hypothalamus-corticotrope- adrenal cortex ensemble. However, we have no a priori reason to assume hypothalamic damage in our patients because they had no previous pituitary irradiation or very large tumors impinging on the hypothalamus. Furthermore, our findings are strengthened by the consecutive nature of the patient series and the yearly assessment of the pituitary function. For the evaluation we used

preferably results of ITT. However, ongoing follow-up after the last ITT did not raise the suspicion of new adrenal deficiencies.

The recurrence of GH overproduction after initial cure by surgery may be due to either regrowth of residual tumor tissue or true recurrence (38–42). In our series we retested all patients cured by surgery at regular intervals. In our experience, recurrence of GH excess may occur, even after many years of postoperative cure documented by repeatedly normal IGF-I levels and normal GH nadir responses during the glucose tolerance test. This was also true after 1993, when a more sensitive GH assay was introduced. Even though this sequence of events may not exclude recurrence from persistent, but apparently longtime subclinical, postoperative adenomatous tissue, this observation indicates that the recurrence rate in our series is not merely the consequence of persistent postoperative disease. Moreover, in patients retested after surgical cure with regular intervals, we have previously documented that biochemical recurrence of GH excess after initial surgical cure clearly precedes radiological recurrence (42). Therefore, even in cases with biochemical recurrence of GH excess, it is highly unlikely that mass effects of adenomatous tissue were present. Finally, in the present study, we included the patients until the start of additional treatment of GH excess in the case of recurrent disease. Therefore, it is unlikely that recurrences of GH excess after years of biochemical remission affect our conclusions.

In conclusion, the incidence rate of late-onset adrenocortical insufficiency after successful surgery for acromegaly is very low (2/1000 person-years). We propose to repeat the dynamic test of HPA function 1 yr after 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 or symptoms suggestive of corticotrope insufficiency, additional dynamic testing should be performed.

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Chapter 6

Pituitary dysfunction in adult patients after cranial radiotherapy: a systematic review and meta-analysis

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Abstract

Context: Cranial radiotherapy is an important cause of hypopituitarism. The prevalence of hypopituitarism varies considerably between studies.

Objective: We conducted a systematic review and meta-analysis of reported prevalences of hypopituitarism in adults radiated for nonpituitary tumors.

Data sources: We searched PubMed, EMBASE, Web of Science and the Cochrane Library to identify potentially relevant studies.

Study selection: Studies were eligible for inclusion with following criteria: 1) cranial radiotherapy for nonpituitary tumors and/or total body irradiation for haematological malignancies 2) adult population (>18 yr old) 3) report on endocrine evaluation.

Data extraction: Data review was done by two independent reviewers. Besides extraction of baseline and treatment characteristics, also endocrine tests; definitions and cut-off values used to define pituitary insufficiency, were extracted.

Results: Eighteen studies with a total of 813 patients were included. These included 608 patients treated for nasopharyngeal cancer (75%) and 205 for intracerebral tumors. The total radiation dose ranged from 14 to 83 and 40 to 97 Gy for nasopharyngeal and intracerebral tumors, respectively. The point prevalence of any degree of hypopituitarism was 0.66 [98% confidence interval (CI), 0.55–0.76]. The prevalence of GH deficiency was 0.45 (95% CI, 0.33–0.57), of LH and FSH 0.3 (95% CI, 0.23–0.37), of TSH 0.25 (95% CI, 0.16–0.37), and of ACTH 0.22 (95% 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 *vs.* intracerebral tumors.

Conclusion: Hypopituitarism is prevalent in adult patients after cranial radiotherapy for nonpituitary tumors. Therefore, all patients treated by cranial radiotherapy should have structured periodical assessment of pituitary functions.

Introduction

Pituitary insufficiency is a late onset sequel of cranial irradiation for intracerebral and nasopharyngeal tumors or total body radiotherapy for hematological malignancies in children (1–9). In the Childhood Cancer Survivor Study (CCSS) 43% of children treated for cerebral tumors had one or more endocrinopathies (10). Consequently, structured follow-up programs for childhood cancer survivors include endocrine assessments. In the last decades, survival rates of patients treated with cranial radiotherapy for various malignancies as well as for benign tumors have improved substantially by introduction of new surgical, radiotherapeutical, and chemotherapeutical options. In contrast to the long-term survivors of cranial radiotherapy in childhood, endocrine surveillance programs have not been routinely incorporated in adults treated with cranial radiotherapy. The prevalence of hypopituitarism after cranial radiotherapy is affected by several factors. First, the time interval between radiotherapy and the assessment of pituitary function is important because the development of pituitary failure is likely to increase in time after radiotherapy (11–13). Second, hypothalamic and pituitary insufficiencies are more likely to develop with increasing radiation exposure (10;14). Finally, methodological differences between the studies with respect to endocrine evaluation, like the use of different endocrine tests with different criteria for pituitary insufficiency, will also affect the prevalence of hypopituitarism.

The aim of this study was to systematically assess the reported prevalence of pituitary insufficiency after cranial or total body radiotherapy for intracerebral tumors, nasopharyngeal tumors or haematological malignancies at the adult age.

Design

Search strategy and eligibility criteria

We searched the following databases for studies on cranial radiotherapy and pituitary failure: PubMed, Cochrane Library, Web of Science, EMBASE, CINAHL database, Academic Search Premier, and Science Direct. The search was performed on August 14, 2010.

In collaboration with a trained clinical librarian, we composed a search strategy for the above mentioned databases, focusing on radiotherapy, pituitary function, cerebral tumors and nasopharyngeal tumors. We used all relevant keyword variations, including free text words. The complete strategy is provided in the Appendix 1. Furthermore, the references of relevant articles were checked for additional articles.

Only original articles in English were included. Studies were eligible for inclusion in this review if they fulfilled the following criteria: 1) cranial radiotherapy for nonpituitary tumors and/or total body irradiation for hematological malignancies 2) >18 yr old at the time of radiotherapy 3) report on endocrine evaluation.

In case of mixed cohorts (*i.e.* including both paediatric and adult patients), patients younger than 18 yr were filtered from the results. In case of duplication of reports involving the same patient cohort the results on the different axes were combined in the analyses and tables, and only the paper with the longest duration of follow-up was included.

Data review and analysis

Initial selection of studies by title and abstract was performed by two reviewers (N.M.A-D en N.E.K.). These studies were retrieved for full assessment. All studies were evaluated by the two reviewers independently. Disagreements were resolved by consensus. Data extraction was based on data from each study provided at the population level. The definition of hypopituitarism had to be stated in the paper, including the endocrine tests used for the evaluation, definitions and cut-off values used to define

pituitary insufficiency for each axis, hormone assays and reference values provided by the authors.

Statistical analysis

The main outcome of the present meta-analysis was the pooled proportion of patients with pituitary insufficiency after cranial radiotherapy. For all studies, the proportion of patients with hypopituitarism was calculated as the number of patients with the pituitary insufficiency divided by the total number of tested patients.

Meta-analysis was performed using an exact likelihood approach. The method used was a logistic regression with a random effect at the study level (15). Given the expected clinical heterogeneity, a random effects model was performed by default, and no fixed effects analyses were performed. For meta-analysis of proportions, the exact likelihood approach based on a binomial distribution has advantages compared to a standard (DerSimonian and Laird) random effects model that is based on a normal distribution. First, estimates from a binomial model are less biased than estimates from models based on a normal approximation (15;16). This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells, whereas the standard approach needs to add an arbitrary value (often 0.5) when dealing with zero-cells. Adding values to zero-cells is known to contribute to the biased estimate of the model (17;18).

Meta-regression analyses were also performed with an exact likelihood approach. A random effects meta-regression was performed to address the question whether the tumor site (nasopharyngeal *vs* intracerebral) influences the prevalence of pituitary insufficiency. All analyses were performed with STATA 10.0 (Stata Corp, College Station, TX, USA).

Risk of bias assessment

An additional evaluation of the risk of bias was performed to identify components that could potentially bias an association between cranial radiotherapy and hypopituitarism. The following study characteristics were evaluated: 1) adequacy of exposure determination, 2) adequacy of inclusion and follow-up, and 3) adequacy of outcome determination. For exposure determination, one point was given if it was stated clearly that

the pituitary was involved in the radiation field, and one point was given if the estimated dose at the pituitary was reported. For the evaluation of inclusion of patients, one point was given for each study that included (consecutive) non-selected patients. For outcome determination, one point was given when the hormonal evaluation also included dynamic tests, and one point was given if all patients in the study were tested. Consequently, each study could attain a maximum score of 5 points. Studies that scored 0–2 points were considered to have a high risk of bias, studies with 2–3 points as intermediate risk, and studies with 4–5 points as studies with a low risk of bias.

Results

Systematic literature search

The initial search resulted in a total of 849 articles (301 in PubMed, four in Cochrane Library, 131 in Web of Science, 353 in EMBASE, 16 in CINAHL database, 27 in Academic Search Premier, and 17 in Science Direct). Of these articles, 616 were unique without duplications (Figure 1). We excluded 378 papers based on title and abstract or language, 157 studies that evaluated patients younger than 16 yr, and seven papers which were not available for evaluation. Consequently, a total of 74 potentially relevant papers were retrieved for full assessment. Of these 74 publications, 51 papers were excluded from further analysis because the studies did not fulfill one or more of the eligibility criteria.

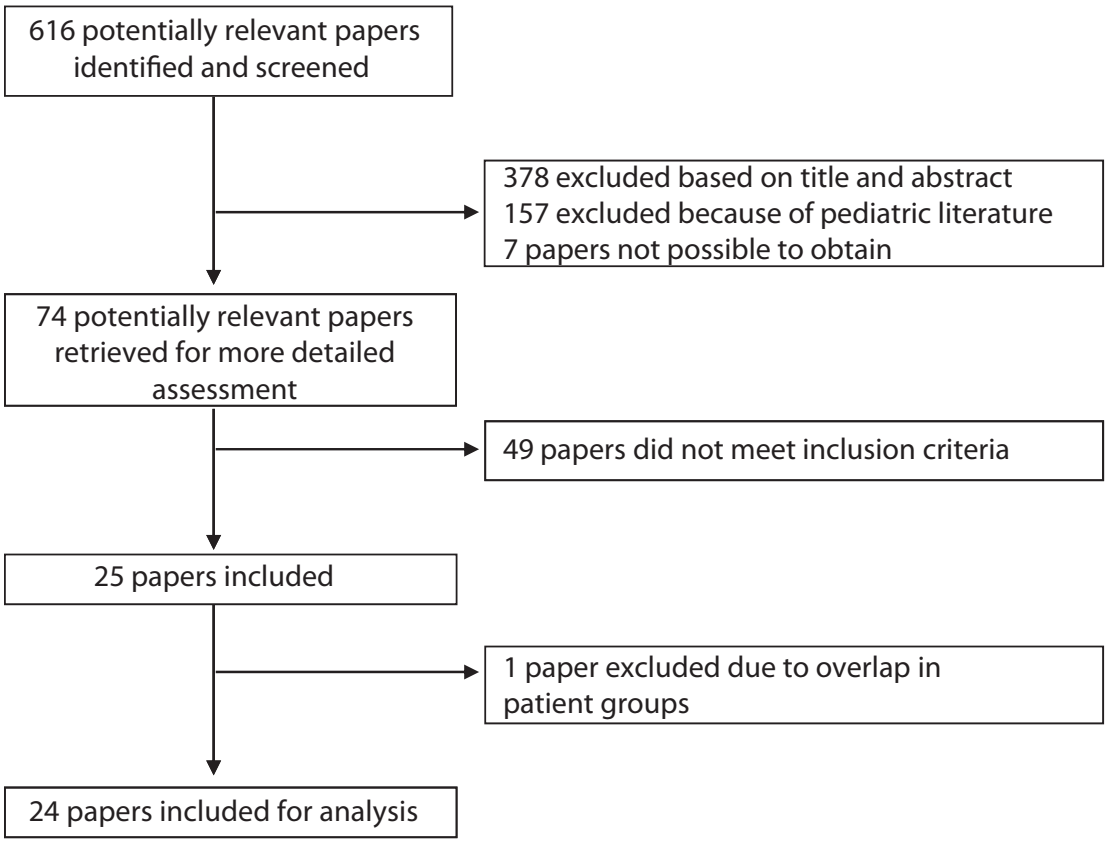

Figure 1. Flowchart of study assessment and exclusion stages

Therefore, ultimately, our search strategy resulted in 23 manuscripts meeting the inclusion criteria. However, some reports described data from the same patient cohort (19–26). In these cases, the results were combined as one study in the analysis, or the study with the longest follow-up was included. Consequently, a total of 18 studies were included in the present review, comprising 813 patients. The number of included patients per study ranged from only six (27) to 312 (20). Five studies included patients younger than 18 yr (26–30). However, in only three of these five studies (27;28;30) it was possible to obtain the numbers of patients treated after the age of 18 yr. The remaining two were included because of the low number of patients younger than 18 yr, or sub-analysis on the patient group younger than 18 yr was performed with no different outcome then the older group (Table 1).

Study characteristics

Details of the 18 included studies are summarized in Table 1 and 2. The studies were published between 1975 and 2009. Seventy-five percent of the patients (608 of 813) were treated for nasopharyngeal cancer (Table 1). The remaining 25% were treated for intracerebral tumors (Table 2). The majority of studies were cross-sectional studies with time after irradiation ranging from 4 months to 30 yr. However, the time after radiation varied considerably between individuals, even within one single study. Two studies did not report the time interval between irradiation and endocrine evaluation (28;31). None of the included papers evaluated patients treated with prophylactic body irradiation in the course of stem cell transplantation for haematological malignancies. In three reports, patient selection criteria were not stated (20;28;31), whereas four studies selected symptomatic patients by recruiting from a radiotherapy complication outpatient clinic or by inclusion of only patients suspected for any degree of hypopituitarism (21;30;32;33). For example, two studies used questionnaires on fatigue or diminished libido in combination with basal hormone samples to select patients for further endocrinological evaluation (22;28).

Table 1. Head and neck tumors

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Snyers, 2009(37)	Total n=32 [a] n=21 endocrine evaluation 56 (28–74) yr	Sinonasal cancer	44–66 Mean dose pituitary = 51–56 Mean dose hypothalamus = 44–52 Chemo n= 23	107 (11–253)	Basal morning serum samples, if abnormal : ITT, ACTH stim test or GHRH-arg	4	62% (13/21)	24% (5/21)	19% (4/21)	14% (3/21)	19% (4/21)	10% (2/21)
Bhandare, 2008(19)[b]	Total n=312 200M/112F n= 112 endocrine evaluation No age mentioned	Nasal cavity n=56 Nasopharynx n=119 Frontal sinus n=2 Etmoid sinus n=5 Sphenoid sinus n=34 Maxillary sinus n=59 Other n=37	Broad range: < 40 – >70 Chemo n= 40	63 (6–365)	Basal serum samples: TSH, fT_4, PRL, GH, Cortisol, LH, FSH, T If abnormal: ACTH-test, metyrapone, CRH test, ITT + vasopressin, GST, GHRH-test, Arginine-test, TRH test	2	60% (67/112)	36% (16/44)	32% (14/44)	70% (31/44)	27% (12/44)	15% (10/68)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Lam, 1991(22)[c]	n=20 22M/9F M: 43.7±8.4 yr F: 36.8±9.0 yr	Nasopharyngeal	Total dose: 60 Estimated dose pituitary: 62	60	Basal serum samples: LH, FSH, PRL, TSH, T_4, T, E_2 ITT, LHRH 100 µg, TRH 200 µg	5	75% (15/20)	55% (11/20)	25% (5/20)	15% (3/20)	35% (7/20)	30% (6/20)
Woo, 1988(31)	n=11 8M/3F Age: 48(33–64) yr	Nasopharyngeal	Estimated dose pituitary: 62–67	72–240	Basal serum samples: LH, FSH, THS, T_4, cortisol, PRL, T, E_2 ITT, LHRH 100 µg, TRH 200 µg	4	82% (9/11)	90% (9/10)	18% (2/11)	45% (5/11)	55% (6/11)	27% (3 /11)
Samaan, 1987(25)[d]	Total n=166 98M/68F Age: 47(6–80) yr	Nasopharyngeal n=114 Paranasal sinus tumors n=29 Optic nerve/ eye tumors n=23	Estimated dose anterior pituitary: 57 (4–75) Estimated dose hypothalamus: 50 (11–75)	12–312	ITT, TRH 500 µg, LHRH 100 µg; Total T_4, T_3 resin uptake	5	75% (124/166)	75% (124/166)	18% (30/166)	20% (33/166)	35%/20% (58/166 FSH) (33/166 LH)	36% (60/166)

Table 1. Continued

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Lam, 1987(21)[e]	n=32 21M/11F n=14 dynamic testing Age: 27–50 yr	Nasopharyngeal	46–60	60–204	n=32 Questionnaires on sexual impairement, galctorroea Basal serum samples: PRL, T_4, FTI, TSH, T If abnormal: E_2, T, ITT, LHRH-test, TRH test	3	25% (8/32)	19% (6/32)	6% (2/32)	13% (4/32)	16% (5/32)	19% (6/32F)
Lam, 1986(20)[f]	n=8 1M/7F Age: 27–52 yr	Nasopharyngeal	46–61 Estimated dose to pituitary: 55–67	>60	Basal serum samples: LH, FSH, TSH, PRL, fT4, E_2, T ITT (n=2), LHRH test, TRH test, GHRH-test (n=6), CRH test (n=4)	5	100% (8/8)	50% (4/8)	50% (4/8)	50% (4/8)	25% (2/8)	88% (7/8)
Huang, 1979(33)	n=11 All females Age: 19–40 yr	Nasopharyngeal	Nasopharyngeal area: 70 Estimated dose HP area: 60–65	12–156	LHRH 25 µg	3	82% (9/11)	NR	NR	NR	82%/64% (9/11 LH) (7/11 FSH)	100% (8/8)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Rosenthal, 1976(34)	n=6 All Male Age: 35–66 yr	Nasopharyngeal	55–65	12–96	Basal serum samples: T_4, TSH, FTI, T_3, cortisol, LH, FSH, GH TRH test, ITT (n=2)	3	67% (4/6)	100% (2/2)	50% (1/2)	67% (4/6)	NR	NR
Samaan, 1975(36)	n=10 7M/3F Age: 26–55 Age Rtx: 41 (8–58 yr)[g]	Nasopharyngeal	Estimated dose HP area: 50–83 50–65 to thyroid lobes (n=12)	60–240	ITT, Chlorpromazin: 25 mg, TRH test 500 µg, LHRH 100 µg, T_4, T_3 resin uptake, 24 hour 131-I thyroid uptake	4	100%	60% (6/10)	50% (5/10)	40% (4/10)	30% (3/10)	50% (5/10)

ACTH, adrenocorticotrope hormone; E_2, estrogens; F, female; FSH, follicle stimulation hormone; GH, growth hormone; GHRH, growth hormone releasing hormone; GST, glucagon stimulation test; Gy, Gray; HPA, hypothalamus pituitary axis; ITT, insulin tolerance test; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; N, number; NR, not reported; M, male; PRL, prolactin; Rtx, radiotherapy; T, testosterone; T_4, thyroxine; T_3, triiodothyronine;TRH, thyreotropin releasing hormone, TSH, thyroid stimulating hormone;

[a] Total population n=168, however only n=32 long term follow-up in late morbidity clinic and n=21 endocrine evaluation

[b] Same patient group as (18): Clinical hypopituitarism: 14.1% (44/312), n=68 had dynamic testing and n=23 (33.8%) had subclinical hypopituitarism

[c] Combination of results with (44) which described follow-up after 2 yrs of same cohort

[d] Part of the results were reported previously in (24). Patients were divided into 2 groups >15 yrs and <15. There was no difference between both groups in pituitary failure after 4 yrs.

[e] All patients received questionnaires; only those with suggested hypopituitarism had detailed endocrine assessment (n=14)

[f] All patients referred because of symptoms of hypopituitarism

[g] n=5 < 16 years during radiotherapy

Table 2. Primary intracerebral tumors

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Schneider, 2006(30)	n= 44 28 M/40 F Age: 45 (20–79) yr	Glioma n= 40 Neuroblastoma n= 1 Menigeoma n= 18 Schwanoma n= 5 Dysgerminoma n= 2 Neuroblastoma n= 1 Chondrosarcoma n= 1 Hemangiopericytoma n= 1 Oesteosarcoma n= 1	NR Chemo n=27	NR	Basal serum samples: cortisol, 24-h urinary cortisol, T_3, T_4, TSH, PRL, FSH, LH, test, E_2 GHRH-arg	2	37% (17/44)	27% (12/44)	18% (8/44)	16% (7/44)	29.5% (13/44)	7% (3/44)
Agha, 2005(35)	n= 56 28 M/28 F Age: 39.3±11.9 yr	Glioma n= 43 Meningeoma n= 5 Pinealoma n= 3 Medulloblastoma n= 2 Other n= 3	Estimated dose pituitary: 54(4–97) Chemo n=7	6	Basal serum samples: FSH, LH, TSH, T_4, PRL, IGF-I, T, E_2 ITT (n=25), Arginine stim test, ACTH stim test	5	41% (23/56)	32% (18/56)	21% (12/56)	9% (5/56)	27% (15/56)	32% (18/56)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irraidiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Johannesen, 2003(28)	n= 33 18M/15F n= 25 endocrine evaluation Age Rtx: 38 (14–68) yr	Low grade glioma n= 27 High grade glioma n= 5 Anaplastic glioma n= 1	54 (45–59)	13.1 (6–25.6)	Basal serum levels If abnormal: TRH test, CRH test	3	64% (16/25)	NR	4% (1/25)	56% (14/25)	16% (4/25)	0
Popovic, 2002(29)	Total n= 22 n= 6 >18 yr	Medulloblastoma n= 4 Pinealoma n= 2	56 Estimated dose pituitary: 25–30	7.6 ± 0.7 (2–13)	ITT, GHRH-GHRP6	3	67% (4/6)	ITT: 67% (4/6) GHRH-GHRP6: 33% (2/6)	NR	NR	NR	NR
Taphoorn, 1995(38)	n= 13 9M/4F Age: 24–66 yr	Low grade astrocytoma n= 7 Low grade oligodendroma n= 6	45–61 Mean calculated dose pituitary 36(0–50)	3 (1–11.5)	Basal serum levels TRH test 200 µg GnRH test 100 µg hCRF test 100 µg GHRH 50 µg	5	77% (10/13)	31% (4/13)	62% (8/13)	0%	15% (2/13)	23% (3/13)

Table 2. Continued

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Constine, 1987(27) [a]	Total n=65 n=30 (>18 yr) Age: 36.5(19–65) yr	Glioma n= 43 Medulloblas n= 7 Meningioma n= 5 Ependymoma n= 4 Others n= 5 No biopsy n= 2	Various amounts n = 47 cranial Rtx n= 18 craniospinal Rtx Chemo n=8	NR	T_4 and TSH n= 65 PRL n= 47 No dynamic tests n= 35 cranial Rtx	1	NR	NR	NR	25% (7/28)	Only measured in 9 people	29% (7/24)
Mechanick, 1986(32)	n= 15 5M/10F Age: 22–59 yr	Astrocytomas n= 14 Medulloblast n= 1	40–50 to whole brain 1–22 local boost Chemo n=13	2–9	PRL n=9,T_4, T_3, T_3-resin uptake TRH 200 µg	2	60% (9/15)	NR	NR	14.3% (1/7)	NR	100% (9/9)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irraidiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Harrop, 1976(26)	Total n=17 n= 8 > 18 yr Group 1 : tumors remote from the HP-area n= 5 3M/2F Group 2: tumors in hypothalamic area n= 3 1M/2F	Astrocytoma: n= 2 Meningeoma: n= 3 Angioma: n= 1 No biopsy: n= 2	40–52	6 (1–15)	ITT (n= 6), GST (n= 6), TRH (n= 8) 200 µg 250 µg Synacthen, Clomiphene stim test (n= 5), LHRH 100 µg	4	62.5% (5/8)	50% (4/8)	12.5% (1/8)	12.5% (1/8)	37.5% (3/8)	NR

ACTH adrenocorticotrope hormone; E_2, estrogens; F, female; FSH, follicle stimulating hormone; GH, growth hormone; GHRH, growth hormone releasing hormone; GST, glucagon stimulation test; Gy, Gray; HPA, hypothalamus pituitary axis; ITT, insulin tolerance test; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; N, number; NR, not reported; M, male; PRL, prolactin; Rtx, radiotherapy; T, testosterone; T_4, thyroxine; T_3, triiodothyronine ;TRH, thyreotropin releasing hormone, TSH, thyroid stimulating hormone;
a Evaluation galactorrhea, libido, menstrual function, texture of skin and hair, weight change, constipation, leg cramping, heat/cold intolerance. When abnormal quationaire: basal hormone levels, 2 patients did fill out questionnaire but did not proceed to testing.

Risk of bias assessment

One study was classified as high risk (received 1 point) (28), eight studies as intermediate risk (20;22;29–31;33–35), and nine studies as low risk for selection bias (21;23;26;27;32;36–39).

Radiotherapy

The radiation dose was reported in all, but one study (31) and ranged from 14 to 83 and 40 to 97 Gy in patients treated for nasopharyngeal carcinomas and intracerebral tumors, respectively. A total of nine studies (six involving patients treated for nasopharyngeal tumors and three for intracerebral tumors) also calculated the estimated dose delivered to the pituitary, ranging from 46 to 83 Gy (in patients treated for nasopharyngeal tumors) and 25 to 97 Gy (in patients with intracerebral tumors) (21;23;26;29;30;36–39).

Endocrine assessment

The overall prevalence of any degree of hypopituitarism differed considerably between the studies, ranging from 25% (22) to 100% (21;37) in studies involving patients treated for nasopharyngeal tumors, and from 37% (31) to 77% (39) in patients treated for intracerebral tumors (Figure 2, Table 1 and 2).

GH-IGF-I axis (n=724)

Fourteen studies evaluated the GH-IGF-I axis. However, in only 61% (440 of 724) of the patients the axis was evaluated using basal serum IGF-I and/or GH levels and/or a stimulation test [glucagon stimulation test, insulin tolerance test (ITT), arginine test, and combined GHRH plus arginine tes] (20–23;26;27;30–32;35–40). The prevalence of GH deficiency varied between 24 and 100%. The prevalence of 100% was assessed in one study of six patients that evaluated only two patients using ITT (35).

Hypothalamic-pituitary-adrenal (HPA) axis (n=751)

The HPA axis was evaluated in 14 studies. In only 61% (460/751) of the patients the axis was tested by basal serum cortisol levels and/or a stimulation test (CRH test, ITT, glucagon or ACTH test). Adrenal insufficiency was diagnosed in 0–50% of patients with nasopharyngeal tumors and in 3–62% of the patients with intracerebral tumors.

Hypothalamic-pituitary-thyroidal-axis (n=488)

Sixteen studies evaluated thyroid function using either basal serum hormone levels or a TRH-stimulation test. TSH deficiency was diagnosed in 26% of the patients (126/488). The prevalence rates ranged from 0 to 67% and 13 to 25% in patients with nasopharyngeal cancers and intracerebral tumors, respectively.

Hypothalamic-pituitary-gonadal axis (n=469)

The pituitary-gonadal axis was assessed in 14 studies. Hypogonadotropic hypogonadism was present in 30% (143/469): in 30–82% of cases treated for nasopharyngeal cancer and in 38–61% of cases treated for intracerebral tumors.

Hyperprolactenemia (n=502)

Prolactin levels were measured in 15 studies, documenting hyperprolactinemia in 144 of 502 patients (29%, 2–100% in patients treated for nasopharyngeal cancers, and 7–100% in patients treated for intracerebral tumors). One study did not use basal prolactin levels for definition of a prolactin secretion disturbance but defined abnormal prolactin secretion as a failure to rise more than three-fold in response to a TRH test (39). Therefore, this study was not included in the analysis on this axis.

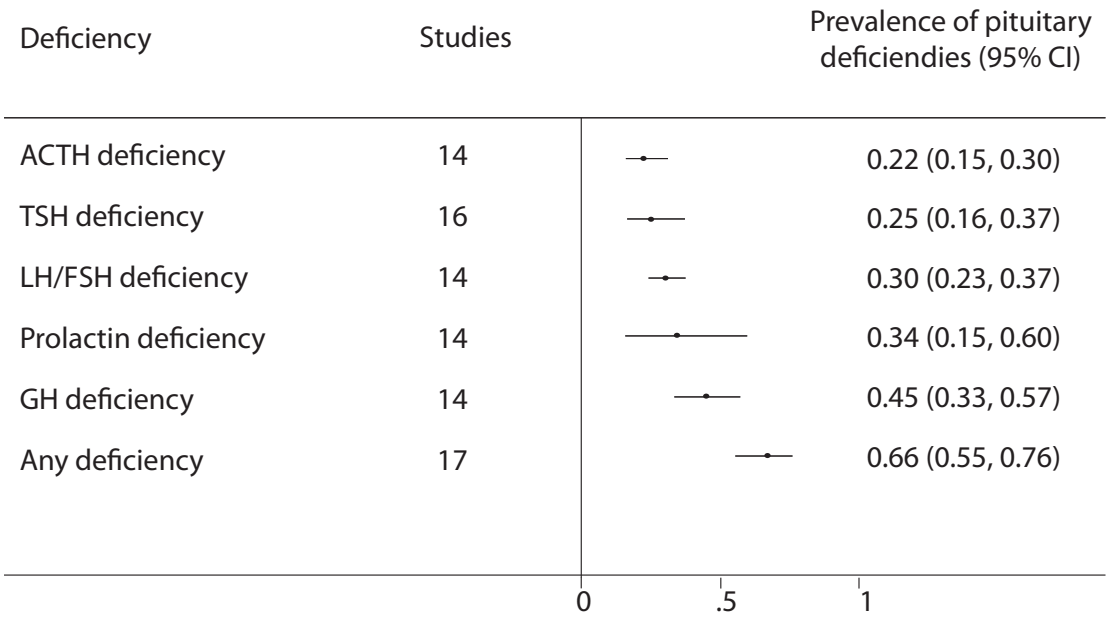

Figure 2A. Random effects meta-analysis of prevalence of pituitary insufficiency after cranial radiotherapy.

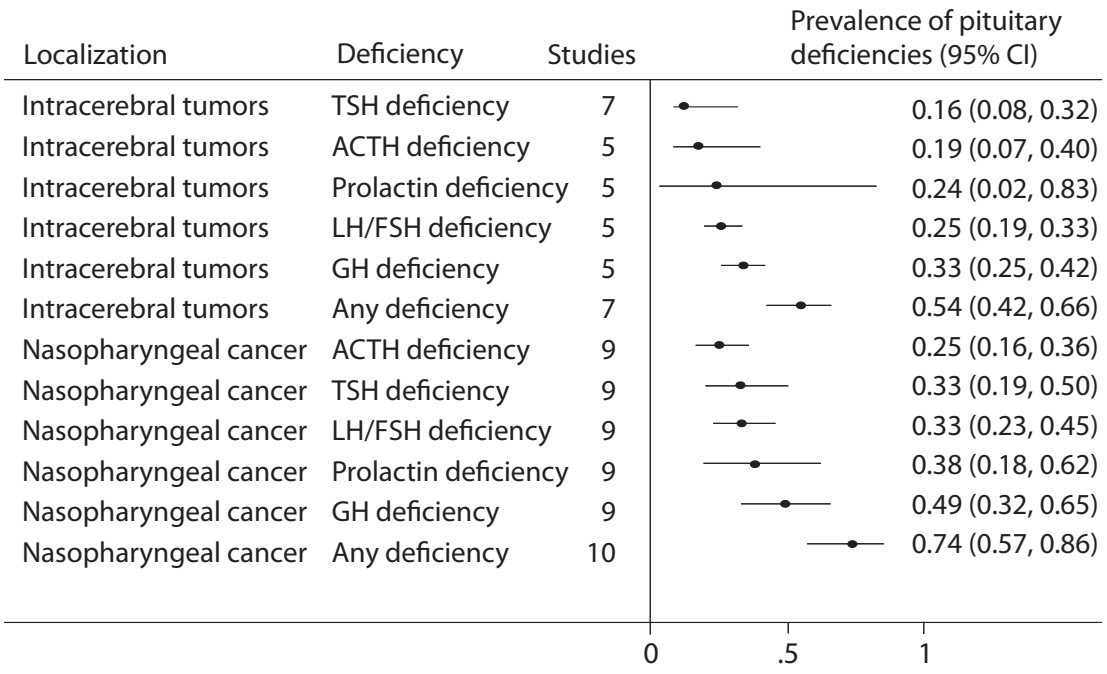

Figure 2B. Random effects meta-analysis of prevalence of pituitary insufficiency according to tumor site

Meta-analysis (Figure 2A and B)

The pooled prevalence of any degree of hypopituitarism was 0.66 [95% confidence interval (CI), 0.55–0.76). GH deficiency was the most prevalent pituitary deficiency, with a prevalence of 0.45 (95% CI, 0.33–0.57), followed by LH/FSH deficiency 0.3 (95% CI, 0.23–0.37) and TSH deficiency 0.25 (95% CI, 0.16–0.37), respectively. The prevalence of hyperprolactinemia was 0.34 (95% CI, 0.15–0.6) and ACTH deficiency had the lowest prevalence 0.22 (95% CI, 0.15–0.3).

In a random effects meta-regression, the effect of tumor localization (nasopharyngeal *vs* cerebral) on the prevalence of deficiencies was assessed. There was no statistically significant association between the probability of any pituitary deficiency ($P = 0.14$), GH deficiency ($P = 0.36$), ACTH deficiency ($P = 0.75$), TSH deficiency ($P = 0.11$) LH/FSH deficiency ($P = 0.21$) as well as hyperprolactinemia ($P = 0.44$) and the indication for radiotherapy (nasopharyngeal cancer *vs.* intracerebral tumors).

A sensitivity analysis with four studies explicitly mentioning the inclusion of consecutive unselected patients was performed (23;29;36). The pooled prevalence of any pituitary deficiency was 0.62 (95% CI 0.45–0.77), which is similar to the pooled prevalence of 0.66 when combining all the studies.

Pituitary insufficiency related to duration of follow-up after radiotherapy

Two studies reported on the occurrence in time of hypopituitarism (23;26). The prevalence of pituitary failure in patients treated for nasopharyngeal tumors was 6% after 1 yr, 35% after 2 yr, 56% after 3 yr and 62% after 4 and 5 yr (23). Samaan *et al.* (26) reported on the classical sequential order of failure of individual pituitary functions in time. GH deficiency occurred after a mean of 2.6 yr, followed by failure of the pituitary-gonadal axis and hyperprolactinemia after approximately 3.8 yr, ACTH insufficiency after 6 yr, and finally TSH insufficiency after a mean of 11 yr.

Discussion

This systematic review and meta-analysis demonstrated that pituitary insufficiency is a highly prevalent condition in adult patients after cranial radiotherapy for nasopharyngeal and intracerebral tumors. The prevalence of any form of hypopituitarism was 0.66 (95% CI, 0.55–0.76). 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 were associated with differences in the number of patients included in the study and the manner of endocrine evaluation.

The risk of development of hypopituitarism after cranial radiotherapy is a well recognized phenomenon in children. The likelihood to develop hypothalamic-pituitary insufficiency increases with increasing radiation exposure and with prolonged duration of follow-up up after radiotherapy (11;12). In the CCSS 43% of pediatric patients treated for cerebral tumors had one or more endocrinopathies (10). Our meta-analysis showed that hypopituitarism is present in approximately two thirds of all adult patients previously treated with cranial irradiation. The prevalence of hypopituitarism after cranial radiotherapy is affected by several factors including radiation dose and techniques. Furthermore, the time interval between radiotherapy and the assessment of pituitary functions is important because the development of pituitary failure is likely to increase during prolongation of follow-up after radiotherapy (11;12).

A random effects meta-regression revealed no significantly different effects of underlying disease on pituitary function between the two groups of adult patients reported in literature; *i.e.* those treated for nasopharyngeal cancer *vs.* intracerebral tumors. In addition, the overall difference in radiation dosage did not differ between groups: 40–83 Gy for the patients treated for nasopharyngeal carcinoma and 40–97 Gy for the patients with intracerebral tumors. The use of different radiotherapeutical techniques, however, will most likely affect the rate of

subsequent hypopituitarism because higher cumulative radiation doses are associated with increasing incidence rates of pituitary failure (11;12).

Patients treated for nasopharyngeal tumors are usually treated with a higher average dosage and additive high dose single tumor boost. Therefore, a separate analysis of the studies concerning nasopharyngeal tumors *vs.* the other studies was performed (Figure 2A). However, there were no significant differences in the prevalence of any pituitary insufficiency between both groups. There are various possible explanations for this lack of significant differences between the two patient groups despite differences in irradiation dose. In nine studies from which the estimated doses delivered to the pituitary could be extracted (six involving patients treated for nasopharyngeal tumors and three for intracerebral tumors), the dose ranges were wide in both patient groups and showed a considerable overlap. In patients treated for nasopharyngeal tumors, the dose ranged from 46–83 Gy, and in patients with intracerebral tumors the dose ranged from 25–97 Gy. Duration of follow-up since radiotherapy varied from 11–253 months in the patient group treated for nasopharyngeal tumors and from 12 – 156 months in the group treated for intracerebral tumors. Finally, the overall prevalence of pituitary insufficiency is already high in both groups with 0.54 (95% CI, 0.42–0.66) for intracerebral tumors *vs.* 0.74 (95% CI, 0.57–0.86) for nasopharyngeal tumors. This 0.2 difference in prevalence, however, did not result in significant differences between groups ($P = 0.14$).

According to our risk of bias stratification, nine studies were considered as being at low risk of bias. The majority of studies used cross-sectional study designs with large differences in the time of evaluation in relation to previous radiotherapy. The selection of patient groups differed largely between the studies. Patient selection criteria were not stated in some of the reports (20;28;31), whereas the description of the selection procedures in other studies suggests preselection of patients, like recruitment from a radiotherapy complication outpatient clinic or by including only symptomatic patients suspected for any degree of hypopituitarism (21;30;32;33). Two studies, (n=186), used a prospective design; the reasons for loss to follow-up were not mentioned in any of the studies, precluding definite answers after 5 yr of follow-up (23;26). We additionally performed a sensitivity analysis of studies that qualified as a potential low – intermediate risk of bias (23;29;36;39). This analysis revealed a pooled proportion of any pituitary deficiency of 0.62 (95% CI,

0.45–0.77), which is remarkably close to the overall found prevalence of 0.66 (95% CI, 0.55–0.76) calculated for all studies. This outcome illustrates that signs and symptoms of hypopituitarism after cranial irradiation apparently are not predictive of hypopituitarism in individual patients with their condition.

Differences in endocrine evaluation may also affect the reported prevalence. The majority of patients were not evaluated by proper stimulation tests. Therefore, it is likely that the estimates of hypopituitarism after cranial radiotherapy represent a rather conservative estimation of the true prevalence of hypopituitarism. In addition, studies that did perform stimulation tests used different tests and cut-off values, and only 10 of 18 studies assessed all pituitary axes (but even then, not all patients were tested for each axis). Moreover, the hypothalamic-pituitary-thyroidal axis and the hypothalamic-pituitary-gonadal axis can also be influenced by the use of alkylating chemotherapeutics and exposure of the thyroid gland and gonads to irradiation (19; 41–43). Primary hypothyroidism in patients treated for nasopharyngeal carcinoma occurs up to 20–30% within the first year after treatment (44). In the random effects regression model the prevalence of TSH deficiency was 0.33 (95% CI, 0.19–0.5), and 0.16 (95% CI, 0.08–0.32) for the patients treated for intracerebral tumors. These differences were not significant, with P=0.11. Hypogonadism after cranial radiotherapy was difficult to quantify because some studies reported testosterone or estrogen levels, whereas others used delayed or insufficient LH/FSH responses to GnRH as a criterion for hypogonadism. In addition, primary gonadal failure is highly prevalent in patients treated with chemotherapy, especially when treated with alkalyting agents which could overestimate the results (41). Patients treated for nasopharyngeal tumors were more likely to receive chemotherapy but, again, no significant differences between groups were found.

Prolactin might be another possible tool to estimate the likelihood of radiation induced damage of the hypothalamic area. Because hyperprolactinemia might be a consequence of decreased hypothalamic dopamine secretion, hyperprolactinemia is variable in severity and often subclinical; it diminishes and might even normalize in time due to slowly evolving radiationinduced damage of lactotrophs. If hyperprolactinemia is to be considered as an indicator of disturbed hypothalamic dopamine secretion, one could expect the prolactin level to be high in the first years

after radiation and normal after several years when lactrotroph function has declined. Unfortunately, none of the studies provided information on prolactin levels in relation to the time interval since radiotherapy.

Considering the high prevalence of hypopituitarism found, 0.66 (95% CI, 0.55–0.76), and that there was no significant difference between groups, assessment of pituitary function should be included in the long-term follow-up of all cranially irradiated patients. Current literature does not provide a timeline or a sequence of axis failure. Hypopituitarism can occur as soon as the first year after treatment, but can also occur 11 yr after treatment (23;26). Taken into consideration the improved survival of patients, duration of follow-up for at least 15 yr should be advisable. This follow-up period should include a basal morning hormone sample and dynamic testing of the HPA axis in every patient not on corticosteroids. Dynamic testing of the somatotrope axis should be defined per patient, since GH failure will not have therapeutical consequences, although it might be an indicator for radiation induced pituitary damage.

This systematic review underscores the need for structured, periodical, endocrine assessments of all patients who survive after cranial radiotherapy for all kinds of diagnosis. Therefore, an increasing number of patients will require a structured tailored periodical evaluation of pituitary functions after cranial radiotherapy.

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Chapter 7

Growth hormone replacement therapy in elderly growth hormone deficient patients: a systematic review

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Abstract

Context: Recombinant human GH (rhGH) is prescribed for the treatment of adultsz with GH deficiency (GHD). However, conflicting data are available on the efficacy of rhGH treatment in elderly GHD patients.

Objective: To assess the efficacy of rhGH treatment in elderly GHD subjects.

Methods: We searched PubMed, Cochrane Library, Web of Science and EMBASE.

Study selection: Eligible studies included GHD patients, aged > 60 years, treated with rhGH. Data extraction was performed by two reviewers independently.

Results: We found 11 eligible studies with a total of 534 patients. Only two studies had prospective, randomized, placebo-controlled study designs of rhGH treatment with a duration of 6 (n=15) and 12 months (n=62), respectively. Treatment with rhGH decreased total and low density lipoprotein (LDL) cholesterol levels by 4–8 and 11–16%, respectively, but did not alter high density lipoprotein or triglyceride levels. RhGH did not affect body mass index, but decreased waist circumference (by ~3 cm) and waist/hip ratio. RhGh did not consistently affect blood pressure or bone mineral density. RhGH increased lean body mass by 2–5% and decreased total fat mass by 7–10% in four studies, but did not affect body composition in two other studies. RhGH consistently improved quality of life (QoL) parameters reflected in AGHDA-scores. There are no explicit data on elderly GHD patients aged > 80 years.

Conclusion: RhGH 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.

Introduction

In healthy adults, GH secretion declines with increasing age (1;2). Some of the clinical features of normal aging resemble the manifestations of pathological GH deficiency (GHD). These features include changes in body composition (BC), such as increased total fat mass, decreased lean body mass (LBM) and decreased bone mass, as well as a higher prevalence of cardiovascular risk factors and diminished cardiac function (3).

Consequently, a number of studies have examined the effect of recombinant human GH (rhGH) on various clinical parameters in otherwise healthy elderly subjects (4) as well as in elderly patients with GHD. Rudman *et al.* (1990) (5) were the first to report that 6 months of rhGH treatment in healthy elderly men reduced adiposity and increased muscle mass and bone mineral density (BMD). Other studies observed similar beneficial effects, suggesting a potential role for rhGH as anti-aging therapy (6–8). A recent systematic review and meta-analysis of randomized controlled trials observed that rhGH treatment decreased overall fat mass decreased by ~2.1 kg and increased overall LBM increased by ~2.1 kg (CI, 1.3–2.9) (P<0.001), without any effect on weight. However, rhGH was associated with increased rates of adverse effects (4). Moreover, in healthy elderly subjects, higher physiological insulin like growth factor-I (IGF-I) concentrations are associated with increased mortality (9). Several studies assessed the clinical benefits of rhGH therapy in elderly GHD patients. Some studies in elderly patients with GHD documented that, rhGH improved QoL (10;11), BC (12–14) and lipoprotein profiles (11, 15, 16), although another study showed no effects (17). A consensus statement on the treatment of GHD adults states that 'the age-related decline in the GH-IGF-I status does not warrant rhGH supplementation, but patients with proved GHD should be treated'. These guidelines indicate that the dose of rhGH should be adjusted with advancing age, because of the normal age-related decline in GH secretion (18). Apparently, there is no clear age limitation in treating elderly GHD adults with rhGH.

The aim of the present study was to critically assess the available literature in order to evaluate the available evidence for treatments of elderly patients with GHD. Therefore, we performed a structured review of the available literature on this subject.

Subjects and methods

Search strategy

We performed a systematic search in the following database: PubMed, EMBASE, Web of Science, Cochrane Library, CINAHL database and Academic Search Premier. The search strategy included three main issues: growth hormone deficiency, age > 60 years and growth hormone replacement therapy. We used all relevant keyword variations, including free text words. This resulted in the following search string: *((("Growth hormone deficiency"[ti] OR "Growth Hormone/deficiency"[Majr] OR "GH deficiency"[ti] OR "Growth hormone deficient"[ti] OR "GH deficient"[ti] OR GHD[ti]) AND ("aged"[mesh] OR elderly[tw] OR oldest old OR Nonagenarians OR Nonagenarian OR septuagenarian OR septuagenarians OR Octogenarians OR Octogenarian OR Centenarians OR Centenarian)) OR (("Growth hormone deficiency"[ti] OR "Growth Hormone/deficiency"[Majr] OR "GH deficiency"[ti] OR "Growth hormone deficient"[ti] OR "GH deficient"[ti] OR GHD[ti] OR "growth hormone deficiency" OR "growth hormone deficient" OR "gh deficiency" OR "gh deficient") AND ("Growth Hormone/administration and dosage"[Mesh] OR "Growth Hormone/therapeutic use"[Mesh] OR "Growth Hormone/therapy"[Mesh] OR ((growth hormone OR growth hormones OR Somatotropin OR Somatotropins) AND (therapy OR therapeutic OR replacement))) AND ("aged"[mesh] OR elderly[tw] OR oldest old OR Nonagenarians OR Nonagenarian OR septuagenarian OR septuagenarians OR Octogenarians OR Octogenarian OR Centenarians OR Centenarian))) AND (English [lang]).* Furthermore, the references of relevant articles were checked for additional articles. The following exclusion criteria were used: age < 60 year, non-GHD subjects, no rhGH therapy.

Data review

The following data were extracted from each study: 1) age, gender and number of patients, 2) the endocrine tests used to diagnose GHD, 3) criteria used to define GHD, 4) duration of treatment and treatment dose, and 6) the effect of GH on individual outcome parameters.

Results

The initial search resulted in a total of 577 articles (527 in PubMed, 3 in Cochrane Library, 15 in Web of Science, and 26 in EMBASE, 0 CINAHL database and 6 Academic Search Premier). Of these 577 articles, 534 were unique without duplications. We excluded 403 papers based on title and abstract (studies on GHD without specific focus on rhGH replacement therapy and/or age < 60 yr (n=326), reviews (n=77)). In 89 additional papers, which included patients with an age> 60 yrs, the individual data of the patients could not be extracted. Two additional papers were not available for evaluation.

Therefore, a total of 40 potentially relevant manuscripts were retrieved for full assessment, of which 26 studies were excluded from further analysis because those studies did not meet one or more of the eligibility criteria (age < 60 yrs, no rhGH therapy, healthy elderly).

Ultimately, the search strategy resulted in a total of 14 manuscripts meeting our inclusion criteria. However, only eight different cohorts of patients were described in these 14 studies, because several studies described data from the same patient cohort. The studies by Götherström *et al.* 2010 (12) and Götherström *et al.* 2005 (19) described the same patient cohort (n=24) after 5 and 10 years of rhGH treatment. The studies by Elzgyri *et al.* (16) and Fernholm *et al.*(13) (n=31) as well as Gill *et al.* (14) and Toogood *et al.*(20) (n=12) also described the same patient cohort. Therefore, the data of these studies are described in combination (12–14;16;19;20). The studies reported from the KIMS database included different numbers of patients in each publication (n=64, n=125, n=135, n=64). Although it is likely that similar patients have been included, the different numbers of subjects preclude combination of the data of these separate studies (10;11;15;21).

Consequently, a total of 11 studies were included in the present review, comprising 534 patients (Figure 1).

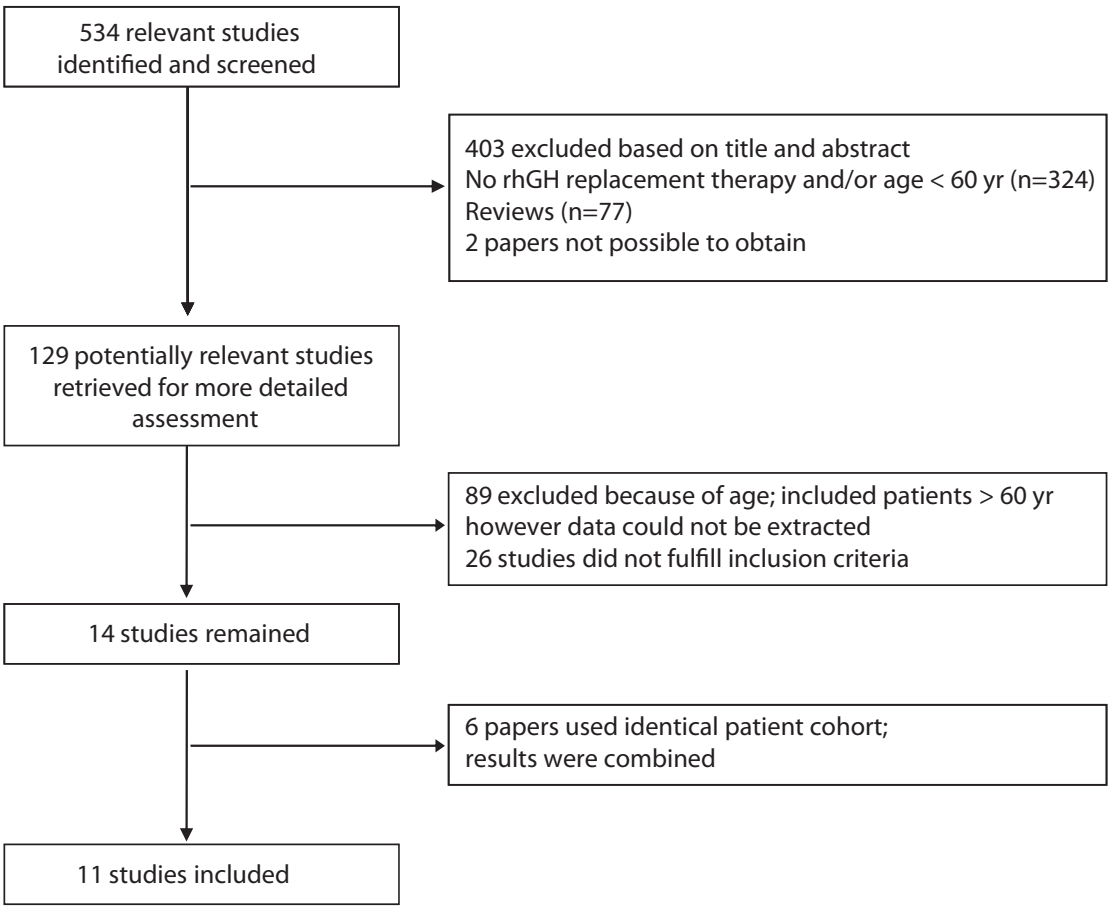

Figure 1. Summary of study assessment and exclusion stages

Study designs

Two studies (n=65) had a prospective placebo-controlled, randomized design assessing the effects of rhGH treatment during 6 (n=15) and 12 n=62) months, respectively, in elderly GHD patients (16;17). The study by Elzgyri *et al.* (2004) (16), that evaluated the effects of rhGH versus placebo for six months, was continued for another 12 months using a nonrandomized prospective study design. The other nine studies had a non-randomized prospective study design, in which the basal data prior to rhGH treatment were used to assess the effects of rhGH (n=469). Four of these studies (n=388) used patients derived from the KIMS database (10;11;15;21).

In this review, we only included studies with patients above the age of 60 years. Two studies did not specify the age of the patient, but only indicate that all patients are >60 years (10;11). One study assessed

patients between the age 60 and 70 years (22), and in three studies, the age ranged between 60 and 75 years (12;21;23). Five studies included patients >75 years and only two of these studies included patients with age >80 years (14–17;24).

Endocrine evaluation

All 11 studies used stimulation tests for the evaluation of GH reserve (Table 1). Different tests, however, were used, including insulin tolerance test (ITT), combined GHRH plus arginine (GHRH-arginine) test, glucagon stimulation test or stimulation with arginine alone (Table 1). The ITT was used in the total population or in the majority of patients in seven studies (11;12;15;17;21–23). The study by Koltowska *et al.* (2009) (10) did not mention which tests were used to diagnose GHD. However, that study also described patients from the KIMS database, and, therefore, it can be assumed that the ITT was also used in the majority of these patients. The remaining three studies either used GHRH tests (16), arginine tests (14) or combined GHRH-arginine tests (24). All but one studies applied the generally used cut-off value for severe GHD of a peak GH < 3 µg/L.

In the study by De Marinis *et al.* (24), which used the GHRH-arginine test, severe GHD was defined as a GH peak < 15 µg/L, without corrections for the effects of body mass index (BMI).

Duration and dose of rhGH treatment

The duration of treatment with rhGH ranged from 6 months (n=15) to 10 years (n=24).

Six studies (n=390) calculated the GH dose based on bodyweight (11;12;15;16;21;24). One of these studies used a predefined dose per kg bodyweight per day (0.0119 mg/kg/day) (12). The other five studies titrated the rhGH dose per kg per week (0.017 – 0.042 mg/kg/wk) (11;15; 16;21;24).

Of the remaining five studies, one study gave three fixed doses of rhGH (0.17, 0.33, and 0.5 mg/day) for 12 weeks. These patients received the highest dose of rhGH, *i.e.* 0.5 mg/day (14). In the remaining four studies, rhGH was titrated on an individual basis with the aim to reach IGF-I levels within the normal age- and sex-related range or clinical improvements, taking QoL and BC into account. The mean dose of rhGH ranged from 0.11 to 0.37 mg/day (11;15;21;24).

IGF-I levels and SD scores

Seven of the 11 studies used age-adjusted IGF-I levels measured in a control population to titrate rhGH dose (11;12;14;16;21–23). Götherström *et al.* and Franco *et al.* 2005 both used the same references values measured in a group of 392 patients aged between 25 and 64 years, as described by Landin-Wilhelmsen *et al.* 1994 (25). Feldt-Rasmussen and Monson and colleagues both refer to a study by Drake *et al.* 1998 (26). However, that study does not mention the IGF-I reference values, but refers to a dose finding study by Janssen and colleagues 1997 (27), in which normative data were based on 54 healthy control subjects aged 20–70 years. The study by Elzgyri *et al.* 2004 use reference values derived from the study by Hilding *et al.* 1999 (28), in which IGF-I values are measured in a population of 448 healthy controls aged 20–96 years. The remaining two studies measure reference values in an own reference population of 450 (18–80 years) (22) and 124 (60–84 years) (14) healthy controls, respectively.

All studies titrated the rhGH dose with the aim of normalizing IGF-I S.D. scores, *i.e.* aiming at IGF-I SDS in physiological levels for age and sex (between -2 and +2). However, four studies also took the clinical response and BC into account for titration of the rhGH dose. Feldt-Rasmussen *et al.* 2004 and Monson *et al.* 2000 both took the clinical response into account when titrating rhGH dose, referring to a study by Drake *et al.* 1998 (26), in which waist/hip (W/H) measurements and improvement of QoL measured by AGHDA were taken into account for the titration of the dose. The remaining two studies (12;23) both state that, when adjusting the rhGH dose, the aim is to 'normalizing IGF-I and BC.', both referring to a study by Johannssen *et al.* 1997 (7), in which individualized doses of rhGH are Q2 compared with doses based on body weight. In their study, normalization of BC was of great importance and normal values derived from a study by Bruce *et al.* 1980 (29), comprising 376 patients in the age 20–70 years, were used to evaluate patients and adjust rhGH levels.

Effects of rhGH on cardiovascular and metabolic parameters

Five studies (n=424) assessed the effects on plasma lipid profiles (11;15;16;21;23). In general, rhGH treatment decreased total and low density lipoprotein (LDL) cholesterol levels by 4–8% (15;16;23) and by 11–16%, respectively, whereas rhGH increased high density lipoprotein

(HDL) only by 17% in one other study (16). Treatment with rhGH did not affect triglyceride (TG) levels at all.

Six studies assessed the effects of rhGH on body weight, height, BMI and/or W/H ratios (11;12;15;21;23;24). In two studies, rhGH did not affect BMI (12;24). In three of five studies which reported W/H ratios, there was a significant decrease in waist circumference (3 cm in de study by Franco *et al.* 2006 (23)) and W/H ratios (11;15;21;23). However, the two other studies did not find any effect of rhGH on W/H ratios (15;24).

Five studies assessed the effects of rhGH on blood pressure (BP) (n=379) (11;15;16;21;23). There were no clear consistent effects of rhGH treatment on BP. Treatment with rhGH did not affect (16), only transiently decreased BP (23), or decreased diastolic BP only (11;15;21).

One study used an exercise test to evaluate cardiac function (n=31). Treatment with rhGH induced a transient increase in heart rate at rest and exercise. However, rhGH treatment did not affect cardiac structural and functional parameters (16).

Effects of rhGH on bone parameters

The effects of rhGH therapy on bone metabolism were evaluated in three studies (n=65). Treatment with rhGH did not affect BMD. One study found that treatment with rhGH increased osteocalcin and calcium levels without any change in PTH levels (23). Another study found that rhGH treatment lowered PTH and urinary cAMP levels, associated with higher adjusted calcium and bone turnover markers, indicating a higher PTH target organ sensitivity (22). The third study observed that treatment with rhGH induced higher markers for bone formation (bone-specific alkaline phosphatase activity, osteocalcin and procollagen I carboxyl-terminal peptide in serum) (13). The effects of rhGH treatment on fracture incidence were not described.

Effects of rhGH on body composition

Six studies assessed the effects of rhGH on body composition using DEXA scan (n=138) (11;12;14;16;23;24). Two studies (n=35) found no effect of rhGH on body composition (23;24). In contrast, the other 4 studies (n=103) found that 6 months of rhGH treatment induced a significant increase in lean body mass (LBM) by 2–5% and a significant decrease in total body fat by 7–10% (12;14;16). Moreover, these effects of rhGH on body composition were reversed, when rhGH therapy was subsequently

stopped (n=12) (14). One study used a four compartment model to assess body fat, body cell mass and extra cellular weight, but these parameters were not affected by rhGH therapy (12;19).

Effects of rhGH on QoL and cognitive functioning

The effects of rhGH treatment on quality of life (QoL) parameters was assessed using only the AGHDA questionnaire in five studies (n=400) (10;11;14;15;21). The majority of these patients were from the KIMS database (n=388). Treatment with rhGH induced significant improvements of AGHDA scores in all studies.

Only one study assessed cognitive functioning (n=34) using computerized psychometric test package (Neurobehavorial Examination-System 2). However, compared with placebo rhGH therapy was not associated with improvement in cognition after 12 months.

Effects of rhGH on muscle strength

One study assessed the effects of 5 and 10 years of rhGH treatment on muscle strength (n=24) (12). Treatment with rhGH induced a transient improvement only in knee flexor strength. However, rhGH treatment protected from most of the normal age-related decline in muscle performance and neuromuscular function.

Adverse effects

Six of the 11 studies mention possible adverse effects of rhGH treatment. In two studies the number of adverse events (AEs) was similar for younger and older patients with GHD (11;15). However, younger patients appeared to have more AEs related to fluid retention (*i.e.* headaches, oedema and arthralgias), whereas patients > 65 yrs had more AEs related to glucose metabolism, cerebrovascular events and neoplasms (11). One of the two placebo-controlled studies mentioned AEs and found no differences between the placebo and rhGH groups (17).

In the study by Fernholm *et al.* 25% of the patients (8/31) developed side effects probably due to fluid retention (peripheral edema, joint stiffness and muscle pain).

However, these side effects subsided spontaneously or after minor dose reduction (13). The study using the highest dose, found AEs in 3 of the 12 patients. The AEs subsided when the dose was down titrated (20). One study needed to reduce the dose of rhGH because of symptoms of the carpal tunnel syndrome (22).

Table 1. Studies on rhGH therapy in GHD elderly patients

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Götherström *et al.*; 2010[12]	n=24 M: 11 65 (61–74) yr	ITT(n=22) GHRH-pyr (n=1) Low IGF-I (n=2)	10 yr	Mean initial dose 0.72 mg/ day in 5 years ↓ 0.37 mg/ day	After 10 yrs: ↑ -1.10(1.08) to 1.17(1.52)	Physical exam. BC (DEXA) Muscle strength*	BW: ↓ Height: ↓ BMI: =	-	-	BF:↓ LBM:↑	-
Götherström *et al.*; 2005[19]		Peak GH < 3 µg/L	5 yr	Aim normalizing IGF-I SDS (-2 to +2) and BC						4-comp model: BF, BCM, and ECW: =	
Koltowska *et al.*; 2009[10]	KIMS n=64 > 60 yr n=286 < 60 yr	ITT Arginine GHRH Glucagon Peak GH < 3 µg/L	6 yr	Mean after 1 yr: 0.26-0.40 mg/ day	Baseline: -1.3(1.19) to -2.1(1.75) After 1 year: 0.8(1.4) to 0.5(1.31)	QoL (AGHDA)	-	-	-	-	Both groups: AGDHA: +

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Feldt-Rasmussen *et al.*; 2004[11]	KIMS n=125 > 65 yr n=2469 < 65 yr M: 1249	ITT Arginine GHRH Glucagon Peak GH < 3 µg/L	12 months	Mean 0.2 mg/ day Titration based on clinical response and IGF-I SDS	Baseline: Between 0 and -4 After 12 months: Between -2 and +2	Physical exam. Lipids BC (DEXA) QoL (AGHDA)	Both groups: Waist (n=114): ↓ W/H-ratio: ↓ BP: < 65 yr: DBP ↓ F > 65 yr: DBP ↓ M	TC (n=107): ↓ LDL: ↓ HDL; TG: =	-	Both groups: LBM (n=47): ↑	Both groups: AGHDA (n=98): +
Monson *et al.*; 2003[21]	KIMS n=135 > 65 yr (65–74) M: 83 n= 1395 < 65 yr	ITT 55% Arginine 14% Glucagon 5% Other 26 % Peak GH < 3 µg/L	12 months	Start dose max 0.042–0.083 mg/ kg/week	Baseline: M: median -1.60 (-3.19 to +0.28) F: median -1.78 (-3.81 to 0.06) After 1 yr: Between -2 and +3	Physical exam. Lipids QoL (AGHDA)	Both groups: Waist (n=93): ↓ W/H-ratio: ↓ BP(n=123): < 65 yr: DBP ↓ F > 65 yr: DBP ↓ M	TC: ↓ LDL (n=78): ↓ HDL; TG: =	-	-	Both groups: AGHDA (n=78): +

Table 1. Continued

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Monson *et al.*; 2000[15]	KIMS n=64 68 (65–82) yr n=863 < 65 yr	ITT 44% Arginine 19% GHRH 13% Glucagon 11% Peak GH < 3 µg/L	> 6 months	Mean: 0.37 mg /day Titration based on clinical response and IGF-I SDS	Between -2 and+2	6 months (n=64): BP QoL (AGHDA) 12 months (n=22): Lipids Bone	Waist: < 65 yr ↓ Only F > 65 yr ↓ BP: > 65 yr: DBP↓ M	TC: ↓ LDL: ↓ HDL; TG: =	-	-	Both groups: AGHDA: +
Sathiavageeswaran *et al.*; 2007[17]	n=34 M: 22 66 (60–77) yr n=16 rhGH n=18 placebo	ITT Arginine Peak GH < 3 µg/L	12 months	Mean: 0.16 mg/day (0.10–0.30) Titration based on IGF-I SDS	Target: Between +1 and +2	Fasting glucose, insulin, HbA1c Cognitive function Mood	HbA1c, insulin, fasting glucose: no differences		-	-	Cognition: No benefits

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Franco *et al.*; 2006[22]	n=24 M: 15 68 (65–75) yr n=24 M: 15 37 (27–46) yr	ITT (n=41) GHRH (n=3), Glucagon (n=1) Peak GH < 3 µg/L	2 yr	Mean: 0.31(0.03) mg/day Normalizing age adjusted IGF-I levels and BC	Target: Between 0 and +2	Physical exam. BC (DEXA) Bone (DEXA) Lipids Glucose metab	Both groups: BW: = Waist: ↓ W/H-ratio: ↓ Transient BP ↓	> 65 yr: LDL: ↓ TC: ↓	Both groups: Osteocalcin :↑ Calcium: ↑ PTH: unaffected BMD: no differences	Both groups: No differences	-
White *et al.*; 2005[23]	n=10 M: 5 60–68 yr n=22 M: 6 26–57 yr	ITT Peak GH < 3 µg/L	12 months	Mean: 0.29(0.03) mg/day Maintaining IGF-I within 2 SD of age related ref range	Baseline: Mean -2.72 ± 1.17 After 1 month: Mean -0.38 ± 0.96	Bone	-		Both groups: PTH target-organ sensitivity: ⊠**	-	-

Table 1. Continued

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Elzgyri *et al.* ; 2004[16]	n=31 M: 25 68 (60–79) yr	GHRH test n=29 ITT n=2 Peak GH < 3 µg/L	6 months GH: n=15 Placebo: n=16 12 months GH: n=28	1 month: 0.017 5 months: 0.033 mg/kg/week 1 month 0.017 11 months 0.033 mg/kg/week Normal range IGF-I assessed by n=448 healthy subjects (20–96 yr)	Baseline: All patients below normal mean for age 6 months: 6.9–18.5 nmol/L (10.4–32.8) 12 months: Mean 18.8+/-1.6	BP, heart rate Lipids ECG Exercise tests	6 and 12 months No changes on cardiac noninvasive structural and functional parameters.	6 months Both groups: TC: ↓ LDL:↓ LDL/HDL ratio: ↓ 12 months TC: ↓ LDL: ↓ HDL: ↑			-

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Fernholm *et al.*; 2000[13]						BC (DEXA) Bone	BP: =		BMD: no changes Markers bone formation: ↑	6 and 12 months: Only in M Placebo: no response GH groups: LBM:↑ TBF:↓	
De Marinis *et al.* ; 2002[24]	n=11 M: 6 60–78 yr n=39 M: 19 18–57 yr	GHRH-arg Peak GH < 15 µg/L	12 months	0.06 – 0.12 IU/ kg/wk Keep IGF-I levels in psychological range for age and sex	NR	BMI Waist BC	BMI: = W/H ratio: =	-	-	No changes	- -

Table 1. Continued

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Gill *et al.* ; 1999[14]	n=12 M: 9 68 (62–85) yr	Arginine Peak GH < 3 µg/L	9 months	Acute study: single bolus 0.1 mg/kg/BW Chronic study: 0.17 mg/day 0.33 mg/day 0.5 mg/day, Each dose 3 months Relationship age and IGF-I assessed in group n=124 (60–87 yr) with specific equations***	Baseline: Between -2 and 0 0.17 mg/day: normal limits 0.33 mg/day: n=2 > +2 0.50 mg/day: n=6 > +2	BC (DEXA) QoL (AHGDA)				FM: ↓ LBM:↑	AGHDA: +

Author	Patients	Definition GHD	Treatment duration	Dose	IGF-I SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthropometrics	*Lipids*	*Bone*	*Body composition*	*QoL/ Cognition*
Toogood *et al.*; 1999						Leptin Insulin BC (DEXA)	Acute study: Leptin: ↑ Insulin: ↑ Chronic study: Leptin: = Insulin: ↑				

AGHD, Assessment of Growth Hormone Deficiency in Adults; BC, body composition; BCM, body cell mass; BF, body fat; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; BW, body weight; DBP, diastolic blood pressure; DEXA, Dual energy X-ray absorptiometry; ECW, extra cellular water; FM, fat mass; GH, growth hormone; GHRH, growth hormone releasing hormone; HDL, high density lipoprotein; IGF-I, insulin-like growth factor –I; ITT, insulin tolerance test; LBM, lean body mass; LDL, low density lipoprotein; M, male; PTH, parathyroid hormone; QoL, quality of life; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; W/H, waist/hip; =, no changes

* Outcome evaluation muscle strength: -Transient ↑ isometric knee flexor strength and ↑ muscle strength reversed age-related decline in muscle strength. Proximal leg muscle responded more markedly than distal arm muscle groups.

** PTH ↓ nephro cAMP ↑ adjusted calcium ↑, bone turnover markers ↑

*** Relationship between age and serum IGF-I is expressed by the following equation: serum IGF-I (µg/L)= (-1.9347 3 x age) + 286.14; sd = 52.67 µg/L.

The age-specific sd score was calculated using the following formula: sd score = [serum IGF-I – (1.9347 3 age)/52.665]

Discussion

This systematic literature review assessed the effects of rhGH treatment in elderly GHD patients. The data indicate that rhGH treatment positively affects total and LDL cholesterol levels, and quality of life parameters. There is controversy about the influence of rhGH therapy on other cardiovascular risk factors, including insulin, HDL-cholesterol and triglyceride levels blood pressure or body composition. Some studies show improvement after treatment with rhGH, whereas others find no changes. Moreover, treatment with rhGH did not improve BMD in elderly subjects with GHD. Finally, studies on the effects of rhGH treatment in elderly GHD patients on clinically relevant endpoints, e.g. cardiovascular morbidity, fractures and mortality, have not been reported.

There is hardly any information on the treatment of very old GHD patients with rhGH. Although 2 studies included patients > 80 years, but data of these patients could not be extracted. Therefore, at present, there is no information with respect to the efficacy and safety of rhGH treatment in GHD octogenarians.

All patients described in the studies included in this systematic review were diagnosed with severe GHD based on different endocrine stimulation tests. However, because of the decline in GH secretion during ageing, aging may have affected the cut-off values of the GH stimulation tests. Studies using the insulin tolerance test (ITT) have been performed in these patients with various results. A study by Finucane *et al.* show that the ITT is a safe test even in elderly patients (30). However, other studies do show a lower GH response to ITT in the elderly (31). Nonetheless, the ITT is contra-indicated in patients with cardiac ischemia or arrhythmias. There are discrepancies between the studies on the cut-off values of the combined GHRH-arginine test and of the arginine test. In previous studies age seemed to be of no influence when using these tests (32;33). However, there is a significantly lower peak GH response in elderly compared to younger patients in the GHRH-arginine test (34). Therefore, the omission to reduce the cut-off values of GH stimulation

tests in aging subjects may result in an erroneous diagnosis of GHD in some of these subjects. It is at present uncertain to which extent this may have affected the conclusions of the studies.

During ageing GH secretion decreases, associated with a decline of IGF-I levels. Therefore, age-adjusted IGF-I SD scores are necessary to be able to assess the treatment response to rhGH. All studies titrated the rhGH dose with the aim of normalizing IGF-I SD scores, *i.e.* aiming at IGF-I SDS in physiological levels for age and sex (between -2 and +2). However, from the analysis described in the results section, it becomes evident that in some studies SD scores were higher. In addition, some studies included the response of body composition to titrate the rhGh dose. Finally, some studies used IGF-I scores from reference populations with a different age distribution. Therefore, there are methological differences between the included studies that may have affected the relation between physiological rhGH replacement and responses in elderly subjects.

In GHD elderly subjects, treatment with rhGH had undisputed positive effects on total and LDL cholesterol levels, and on QoL (10;11;14;15;21). Treatment with rhGH decreased total and LDL-cholesterol levels by 4–8 % and 11–18 %, respectively. RhGH decreased W/H ratio in 3 of the 5 studies that report this parameter, but this was not confirmed in 2 other studies. RhGH increased lean body mass (LBM) by 2–5% and decreased fat mass by 7–10% (12;14;16) in 4 studies (n=192) (11;12;14;16), but this was not confirmed in 2 other studies (n=35) (23;24). One study documented that these positive effects of rhGH on body composition were reversed when rhGH therapy was subsequently stopped, even after only 3 months (n=12) (14). Therefore, there are undeniable effects of rhGH substitution in elderly subjects with GHD for some, but not all, parameters.

Several animal models of GH deficiency show prolonged, rather than decreased, longevity. Mice with mutations that cause GHD or GH resistance, live longer than their genetically normal siblings (9;35–38). In addition, adult body size, which can be considered a biological outcome marker of GH actions, was negatively correlated with longevity in other species, including rats (39), horses (40) and domestic dogs (41;42). Therefore, from an evolutionary perspective the natural decrease of GH and IGF-I levels during normal aging may even be beneficial. Epidemiological studies in humans, however, documented an association between both decreased and increased IGF-I levels and

increased mortality, indicating that the optimal relation between IGF-I and rhGH dose may not be simple (9;43). 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 the elderly. These studies show relatively limited effects. Therefore, the question remains whether the treatment with rhGH is clinically relevant in elderly, and especially very old, patients with GHD.

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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.

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Chapter 9

Nederlandse samenvatting

Inhoud

I. Inleiding

Voor de beoordeling van de functie van de hypofyse zijn diverse diagnostische testen beschikbaar. Er kan gebruik gemaakt worden van basale hormoonspiegels, maar ook van hormoon stimulatietesten. Voor de beoordeling van de schildklier-as, de gonadotrope-as en het prolactine is het voldoende om basale (niet-gestimuleerde) hormoonspiegels te bepalen vroeg in de ochtend (8–9 uur) en daarbij rekening te houden met de klinische symptomen van de patiënt. Echter, de afgifte van cortisol kenmerkt zich door een sterk dag-nacht ritme terwijl de groeihormoon (GH) secretie wordt gekenmerkt door afgifte in pulsen. Voor de beoordeling van de hypofyse bijnier- en GH-IGF-I as is het dus niet mogelijk alleen basale serum hormoonspiegels te bepalen. Voor de juiste evaluatie van deze assen is het gebruik van een stimulatie test noodzakelijk.

Er zijn verschillende stimulatietesten beschikbaar, waarvoor verschillende afkapwaarden worden gebruikt. Wanneer er gebruik wordt gemaakt van een stimulatietest is het van belang rekening te houden met verschillende factoren die van invloed kunnen zijn, zoals leeftijd, geslacht, body mass index (BMI) en medicatiegebruik. Uit onderzoek is gebleken dat met vorderende leeftijd en hogere BMI de secretie van GH afneemt, resulterend in lagere GH spiegels.

Na traumatisch hersenletsel, een operatie aan de hypofyse, of bestraling van de hypofyse kunnen zowel de hypofyse als de hypothalamus beschadigd raken, met uitval van de hypofysefuncties (hypopituïtarisme) als gevolg. Uit onderzoek is echter gebleken dat hypofyseweefsel in staat is te herstellen. Dit gebeurt voornamelijk binnen het eerste jaar na trauma en/of operatie. Wanneer in deze periode een stimulatie test wordt gebruikt om de functie van de hypofyse te bepalen, kan dit dus tot een verkeerde interpretatie van de uiteindelijke restfunctie van de hypofyse leiden.

Het doel van dit proefschrift is om beter inzicht te krijgen in de complexiteit van de verschillende testen die beschikbaar zijn voor

de evaluatie van de hypofysefuncties bij verschillende aandoeningen die gepaard kunnen gaan met passagière of persisterende schade aan de hypofyse en/of de hypothalamus. Het effect van het gebruik van verschillende endocriene testen op de gevonden mate van uitval wordt hierbij kritisch tegen het licht gehouden. Ook is dit proefschrift bedoeld om beter inzicht te krijgen in de behandeling van patiënten met hypofyse uitval.

II. Evaluatie van de functie van de hypofyse na traumatisch hersenletsel

Patiënten die een traumatisch hersenletsel hebben ondergaan kunnen persisterende, invaliderende klachten hebben die lijken op de klachten van patiënten met hypopituïtarisme (zoals verminderde cognitie, depressie, vermoeidheid en een verminderde kwaliteit van leven (QoL)). Het kan dan ook zo zijn dat aanwezige, maar niet gediagnostiseerde uitval van de hypofysefuncties na trauma bijdraagt aan de klachten van deze patiënten. De behandeling van hypopituïtarisme is relatief makkelijk (toedienen van de ontbrekende hormonen) en uit onderzoek is gebleken dat de behandeling de kwaliteit van leven significant kan verbeteren. Het is dus van belang hypopituïtarisme bij patiënten na een hersentrauma vast te stellen, dan wel uit te sluiten.

In de afgelopen jaren is er veelvuldig onderzoek gedaan naar de relatie tussen traumatisch hersenletsel en hormoonuitval. Hierbij hebben verschillende onderzoeken een hoog percentage hypofyse-uitval na TBI beschreven. Er is echter wel een grote variatie in deze beschreven prevalentie. Tijdens de beoordeling van de functie van de hypofyse na hersentrauma is het van belang rekening te houden met de volgende factoren die van invloed kunnen zijn: het tijdsinterval tussen trauma en de endocriene beoordeling, het type en de ernst van het trauma, maar ook de methoden (d.w.z. endocriene testen en criteria) die gebruikt worden om de diagnose hypopituïtarisme te stellen. Sommige studies hebben geconcludeerd dat hypopituïtarisme een veel voorkomende complicatie is na TBI, maar zij hebben geen rekening gehouden met de grote variabiliteit in diagnostische testen en definities van hypofyse uitval. Het doel van onze systematische review in **hoofdstuk 2** was

dan ook om kritisch te kijken naar de gebruikte stimulatie testen en de definities van hypopituïtarisme van studies die hebben gekeken naar de lange termijn uitkomsten na hersentrauma.

Uit onze review blijkt dat er inderdaad een grote variatie bestaat tussen de gerapporteerde prevalentie cijfers, waarschijnlijk gebaseerd op de grote verschillen in endocriene en analytische methoden. De studies in de review gebruiken verschillende stimulatie testen, afkapwaarden en analytische methoden. Bovendien is geen rekening gehouden met factoren die mogelijk van invloed kunnen zijn, zoals BMI. Dit is vooral van belang voor de beoordeling van de GH-IGF-I-as, aangezien de concentratie GH daalt met een hogere BMI. Dit kan resulteren in een overschatting van het percentage GH uitval na TBI bij patiënten met overgewicht. Al deze verschillen maken het moeilijk de resultaten van studies over TBI te vergelijken. Er is meer onderzoek nodig naar voorspellende factoren voor het optreden van hypopituïtarisme na TBI.

Naar aanleiding van de grote variatie in prevalentie cijfers en de variatie in de endocriene en analytische methoden om de hypofyse functies te beoordelen, hebben we in **hoofdstuk 3** onderzoek gedaan naar de lange termijn consequenties bij een grote groep patiënten na hersentrauma. In dit onderzoek hebben we 112 patiënten geïncludeerd die in het verleden traumatisch hersenletsel hadden opgelopen. De patiënten moesten minstens drie dagen in het ziekenhuis hebben gelegen en het trauma moest meer dan een jaar geleden plaats hebben gevonden. Vijf verschillende ziekenhuizen in Nederland hebben geparticipeerd in dit onderzoek. De functie van de hypofyse werd geëvalueerd middels nuchtere basale hormoonspiegels in combinatie met een insuline tolerantie test (ITT n = 90) of, wanneer een ITT gecontraïndiceerd was, een ACTH stimulatie en/of CRH stimulatie test en een gecombineerde GHRH-arginine test (n = 22).

Uit dit onderzoek bleek dat de prevalentie van hypopituïtarisme na traumatisch hersenletsel na lange follow-up laag was. Wanneer gebruik wordt gemaakt van de gouden standaard test (de ITT) voor de evaluatie van GH- en cortisol secretie in de meerderheid van de patiënten, vonden wij een percentage hypofyse uitval van slechts 5.4% (een ernstige groeihormoondeficiëntie (2.8%), hypogonadisme (0.9%), bijnierinsufficiëntie (1.8%)). Dit percentage uitval is veel lager in vergelijking met de prevalentie cijfers gerapporteerd in eerdere

soortgelijke studies (15–90%). Dit kan worden verklaard door het gebruik van verschillende endocriene testen en verschillende afkapwaarden om de diagnose hypopituïtarisme te stellen. Waar mogelijk hebben wij in onze studie gebruik gemaakt van de gouden standaard test: de ITT. In overeenstemming met onderzoek verricht door Klose en collegae, resulteerde dit in een lage prevalentie van GHD en bijnierinsufficiëntie. Als de ITT was gecontraïndiceerd, gebruikten we de gecombineerde stimulatie met GHRH en arginine voor de beoordeling van de GH-as. Het is aangetoond dat dit een goede alternatieve test is, mits de gebruikte afkapwaarden worden aangepast aan de BMI. In ons onderzoek hebben we wel gebruik gemaakt van aangepaste afkapwaarden.

Naast verschillen in endocriene testen, kan ook het tijdsinterval tussen trauma en de endocriene evaluatie, alsook de ernst van het trauma van invloed zijn op de gerapporteerde prevalentie cijfers. In de acute fase na een traumatisch hersenletsel zijn voorbijgaande hormoonveranderingen die lijken op hypopituïtarisme veelvuldig beschreven. Om te voorkomen dat dit van invloed zou kunnen zijn op de endocriene evaluatie in onze studie hebben wij alle patiënten minimaal een jaar na trauma geëvalueerd. Een ernstig trauma verhoogt het risico van het optreden van hypofyse uitval, zodat we tevens besloten hebben om in onze studie alleen patiënten met een ernstig trauma te evalueren. We hebben derhalve alleen patiënten geïncludeerd met een opname duur (ten gevolge van het trauma) van minstens drie dagen. Daarnaast is de Glasgow Coma Scale (GCS) ten tijde van opname beoordeeld om een indruk te krijgen van de ernst van het trauma. Ondanks het feit dat wij met al deze factoren rekening hebben gehouden, bleek het percentage hormoonuitval uiteindelijk toch laag.

Als er sprake is van hypofyse-uitval, kan behandeling hiervan van levensbelang zijn en een aanzienlijke verbetering van de kwaliteit van leven geven. Daarom is het van belang om vooralsnog bij elke patiënt rekening te houden met mogelijke uitval van hypofysefuncties na hersentrauma, ondanks het feit dat op basis van onze resultaten dit mogelijk niet-frequent voorkomt. Bovendien is het van belang dat er consensus komt voor een meer uniforme endocriene evaluatie van hypofysefuncties in het algemeen, en na traumatisch hersenletsel in het bijzonder.

III. Dynamisch testen van de hypofysefunctie bij andere hypofysaire aandoeningen

Hypofyse adenomen kunnen behandeld worden middels transsfenoidale chirurgie (TS), aanvullende radiotherapie en/of medicatie. Een complicatie die kan optreden ten gevolge van de tumor zelf (compressie), of als gevolg van de behandeling (chirurgie en/of radiotherapie) is uitval van de hypofysefuncties. Voor een passende behandeling van patiënten met hypofyse adenomen is het daarom van essentieel belang de functie van de hypofyse te beoordelen ook na operatie en na bestraling.

Endocriene evaluatie na hypofyse operatie

Na TS is het van groot klinisch belang om de hypothalamus-hypofyse-bijnieras (HPA as) te beoordelen, aangezien het belangrijk is te weten of de patiënt bijnierschorshormoon (hydrocortison) afhankelijk is. De gouden standaard test voor de evaluatie van de HPA as is de ITT. Als de ITT vanwege contra-indicaties (epilepsie en/of coronair lijden) niet kan worden uitgevoerd, zijn er verschillende andere dynamische testen beschikbaar, zoals de metyrapon test, de ACTH stimulatie test en de corticotrofine releasing hormoon (CRH) test. Sinds 1990 wordt in ons ziekenhuis de bijnierfunctie van patiënten direct na hypofyse operatie beoordeeld door stimulatie met CRH. Op basis van de testuitslag wordt vervolgens besloten of de patiënten met of zonder hydrocortison substitutietherapie naar huis wordt ontslagen. Gebaseerd op onze klinische ervaring is dit een goede test om de patiënten te screenen op uitval van HPA as. Er is echter weinig literatuur beschikbaar met

betrekking tot de klinische toepasbaarheid van de CRH test direct na TS. Daarom hebben we in **hoofdstuk 4** gekeken naar de klinische toepasbaarheid van deze test bij patiënten behandeld voor niet-ACTH producerende hypofyse-adenomen in ons ziekenhuis.

We hebben retrospectief gekeken naar data van alle patiënten behandeld met TS in ons centrum. In totaal hebben we 144 niet-Cushing patiënten geïncludeerd van wie gegevens beschikbaar waren met betrekking tot de CRH test direct na operatie, van wie tijdens de follow-up periode een bevestigingstest beschikbaar was en waarbij geen sprake was van het gebruik van exogene glucocorticoïden, of een tweede behandeling (zoals heroperatie of aanvullende radiotherapie) die een vergelijk met de eerste test onmogelijk zou maken.

Op basis van de CRH test bleek er bij 42 patiënten sprake te zijn van hypocortisolisme. Echter, 13 van deze patiënten (31%) bleek uiteindelijk, op basis van de bevestigingstest, geen uitval van de HPA as te hebben. Hierbij kon de hydrocortsion suppletie worden gestopt. Een mogelijke verklaring voor deze discrepante resultaten is het gebruik van verschillende afkapwaarden. Voor de ITT zijn er alom geaccepteerde afkapwaarden beschikbaar. Daarentegen, voor de CRH stimulatie test zijn er verschillende afkapwaarden gedefinieerd die allemaal resulteren in een andere sensitiviteit en specificiteit van de test. In ons ziekenhuis wordt de CRH test als screeningstest gebruik om hypocortisolisme direct na TS op te sporen. Wij gebruiken daarom een stringente en hoge afkap waarde van 550 nmol/L. Echter, het streven naar een sensitieve test gaat ten koste van de specificiteit van een test. Hierdoor zal dus een grotere aantal patiënten onjuist als bijnierinsufficiënt worden gediagnosticeerd. Een andere verklaring zou het herstel van de HPA as kunnen zijn. Een recente studie heeft drie en twaalf maanden na TS de HPA as beoordeeld middels ITT. Hieruit bleek dat er binnen het jaar herstel was opgetreden van de HPA as. In overeenstemming met deze studie hebben wij ook 8 patiënten die in eerste instantie gediagnosticeerd waren met bijnieruitval, maar waarbij binnen een jaar na chirurgie herstel van de HPA as optrad. Dit toont aan dat een langdurige, uitgebreide follow-up van patiënten na TS van belang is.

Bij 102 patiënten bleek er direct na TS sprake te zijn van een normale functie van de HPA as. Echter, bij 14 van deze patiënten bleek dat er alsnog sprake was van hypocortisolisme op basis van een tweede test. Deze discrepante resultaten kunnen potentieel levensbedreigend zijn,

aangezien deze patiënten at risk zijn voor het optreden van een adrenale crisis. Waarschijnlijk speelt uitval van overige hypofyse assen hierbij een rol, daar 13 van deze 14 patiënten namelijk ook uitval bleken te hebben van andere hypofyse hormonen. Uit onderzoek is gebleken dat GH en TSH deficiëntie van invloed kunnen zijn op deze testuitslagen. Bovendien kan rhGH therapie bij patiënten met GHD ook een belangrijke rol spelen, vanwege de invloed van GH op het cortisol metabolisme. Groeihormoon stimuleert een enzym dat cruciaal is voor de werking van cortisol op weefselniveau, het 11-β hydroxysteroid dehydrogenase (11βHSD-1), dat de omzetting van cortisol-cortison reguleert. Het gebruik van rhGH bij GHD patiënten kan daarom een cortisol deficiëntie ontmaskeren.

Op basis van onze resultaten concluderen wij dat de CRH test veilig kan worden gebruikt om te evalueren of een patiënt na TS met of zonder HC naar huis kan worden ontslagen. Desalniettemin is de CRH test niet bij alle patiënten een betrouwbare voorspeller. Wij adviseren daarom om de HPA as tijdens follow-up middels een tweede test te evalueren, bijvoorbeeld 3–6 maanden na operatie. Bij patiënten met een verminderde reactie van cortisol op CRH direct postoperatief, die uitval van meerdere hypofyse hormonen blijken te hebben, is hertesten niet noodzakelijk.

In **hoofdstuk 4** hebben we retrospectief gekeken naar alle patiënten die behandeld zijn met TS in ons centrum. In **hoofdstuk 5** hebben we ons gericht op een specifieke groep patiënten; patiënten behandeld met TS voor een GH producerende tumor d.w.z. patiënten met acromegalie. De aanleiding voor ons onderzoek was een recente studie van Ronchi en collegae die de functie van de HPA as bij acromegalie patienten behandeld middels TS hebben onderzocht. Zij vonden een opmerkelijk hoge prevalentie bijnierinsufficiëntie (32%) bij deze patiënten. Zij concludeerden dat de functie van de HPA as kan afnemen na verloop van tijd en dat deze as dus zorgvuldig tijdens follow-up na behandeling gecontroleerd moet blijven worden in alle acromegalie patiënten, ongeacht de aard van de behandeling. Deze aanbeveling heeft duidelijk gevolgen voor de lange termijn behandeling van patiënten met acromegalie. Het doel van **hoofdstuk 5** was dan ook om de prevalentie van bijnierinsufficiëntie na lange termijn follow-up te bepalen in ons eigen cohort van patiënten met acromegalie in remissie na behandeling met TS. We hebben retrospectief gekeken naar de gegevens van 91 patiënten in remissie na TS waarbij de HPA as was beoordeeld met behulp van de

ITT, CRH stimulatie, metyrapon- of ACTH stimulatie test. In ons cohort bleek er bij 16 patiënten (18%) in de direct postoperatieve periode sprake te zijn van bijnierinsufficiëntie. Dit bleek van voorbijgaande aard te zijn bij 8 patiënten en blijvend bij de overige 8 gedurende het eerste jaar na operatie. Dus een jaar na operatie was de prevalentie bijnierinsufficiëntie uiteindelijk slechts 9%. Slechts bij drie patiënten ontstond alsnog een bijnierinsufficiëntie 13, 18 en 24 jaar na de operatie. De incidentie van late bijnierinsufficiëntie na een succesvolle operatie was dus slechts 2 / 1000 persoonsjaren. De prevalentie van bijnierinsufficiëntie bij patiënten in remissie na chirurgie voor acromegalie na langdurige follow-up (mediane follow-up 8.1 jaar (range 1–31 jaar)), was 12%. Op basis van onze gegevens kunnen wij zeggen dat het ontstaan van bijnierinsufficiëntie na TS niet vaak voorkomt.

Het verschil in prevalentie tussen onze studie en de studie van Ronchi en collegae kan worden verklaard door verschillen in onderzoeksopzet en patiëntenpopulatie, maar ook door verschillen in patiëntenselectie en chirurgische technieken. In ons cohort hebben we in de meerderheid van de patiënten gebruik gemaakt van de gouden standaard test (ITT) en een CRH test terwijl in de studie van Ronchi gebruik is gemaakt van een lage dosis ACTH test. Daarnaast zouden de volgende factoren ook mogelijk van invloed kunnen zijn: een veranderd niveau van cortisol bindend globuline (CBG) in acromegalie, de aanwezigheid van postoperatieve GH deficiëntie en de mogelijkheid van herstel van preoperatieve bijnierinsufficiëntie na TS.

Beperkingen van onze studie zijn de retrospectieve aard van de studie en het feit dat de HPA as is beoordeeld middels verschillende cortisol stimulatie testen. Dit doet echter geen afbreuk aan onze conclusies, omdat de ITT, CRH en metyrapon tests allen worden geaccepteerd als test voor de evaluatie van de HPA-as.

Op basis van onze gegevens stellen wij voor om de HPA as een jaar na operatie opnieuw dynamisch te testen bij alle patiënten met postoperatie HPA insufficiëntie. Verder onderzoek is nodig om te beoordelen of jaarlijks basale cortisol waarden kunnen volstaan om de bijnierfunctie te monitoren bij asymptomatische patiënten. Wanneer er echter sprake is van lage basale cortisol spiegels, symptomen van corticotrope insufficiëntie of overige hypofyse uitval, moeten aanvullende dynamisch testen van de HPA as worden uitgevoerd.

Endocriene evaluatie na craniële radiotherapie

Patiënten met niet-hypofysaire hersentumoren en/of tumoren in het neus- en keel gebied worden vaak behandeld met radiotherapie. Tijdens deze behandeling ligt de hypofyse ook in het bestralingsgebied wat kan resulteren in hypofyse insufficiëntie. Voor kinderen is dit een goed beschreven complicatie na radiotherapie. Echter voor volwassenen is de beoordeling van de hypofysefunctie nog niet opgenomen in de richtlijnen voor de follow-up van deze patiënten. In **hoofdstuk 6** rapporteren we een systematisch review waarbij we hebben gekeken naar de prevalentie van hypofyse insufficiëntie na craniële radiotherapie voor niet-hypofysaire tumoren bij volwassen patiënten.

We hebben uiteindelijk slechts 18 studies (n=813) kunnen includeren. Er zijn grote verschillen in de gerapporteerde prevalentie van hypopituïtarisme na craniale radiotherapie, variërend van nauwelijks effect op de hypofyse functie tot bijna 100% van de patiënten met uitval.

Het verschil in prevalentie kan worden toegekend aan verschillen in radiotherapeutische technieken, verschil in studie design, tijdstip van de evaluatie, selectie van patiënten en de verschillen in endocriene evaluatie. Bij de meerderheid van de patiënten werd geen gebruik gemaakt van hormoon stimulatietesten om de hypofysefunctie te beoordelen. Wanneer er wel gebruik werd gemaakt van stimulatietesten, werden er verschillende afkapwaarden en diagnostische criteria gebruikt. De uitgevoerde meta-analyse toonde aan dat er bij ongeveer tweederde van alle volwassenen sprake is van enige vorm van hypofyse-uitval (0.66, 95% CI 0.55–0.76). De prevalentie van groeihormoondeficiëntie was 0.45 (95% CI 0.33–0.57), van LH en FSH 0.3 (95% CI 0.23–0.37), van TSH 0.25 (95% CI 0.16–0.37), en van ACTH 0.22 (95% CI 0.15–0.3). De prevalentie van hyperprolactinemie was 0.34 (95% CI 0.15–0.6). Er waren geen verschillen tussen de effecten van radiotherapie voor nasofaryngeale versus intracerebrale tumoren. Op basis van deze gegevens kunnen we concluderen dat hypopituïtarisme een veelvoorkomende complicatie is ook bij volwassen patiënten die behandeld zijn met craniële radiotherapie. Gezien deze hoge prevalentie zou de evaluatie van hypofysefuncties moeten worden opgenomen in de richtlijnen voor de follow-up van alle patiënten behandeld met craniële radiotherapie.

IV. Behandeling van GHD

Groeihormoon deficiëntie (GHD) kan behandeld worden door toediening van recombinant GH (rhGH). Echter bij de behandeling van patiënten met GHD moet onder andere rekening worden gehouden met de leeftijd aangezien de normale afgifte van GH afneemt met de leeftijd.

In **hoofdstuk 7** hebben we kritisch gekeken naar de beschikbare literatuur met betrekking tot de behandeling van de oudere GHD patiënt. We hebben gezocht naar artikelen die de effecten van rhGH bij patiënten boven de 60 jaar hebben geëvalueerd. Uiteindelijk konden we 11 bruikbare studies met een totaal van 543 patiënten meenemen in onze review. De studies laten zien dat er inderdaad een positief effect op totaal- en LDL-cholesterol is en dat ook de kwaliteit van leven bij deze patiënten verbeterd. Voor de overige uitkomstmaten wordt er echter geen positief effect beschreven. Ook zijn er geen gegevens over het effect van rhGH op klinisch relevante eindpunten zoals hart- en vaatziekten of het voorkomen van botbreuken.

Bij de beoordeling van het effect van rhGH therapie bij oudere patiënten moet rekening worden gehouden met verschillende factoren. Allereerst is het van belang rekening te houden met het feit dat met toenemende leeftijd, de GH productie en dus secretie afneemt. Deze afname kan invloed hebben op de uitkomsten van de stimulatietesten en indirect zal het dus ook van invloed zijn op de afkapwaarden die worden gebruikt. Studies die hebben gekeken naar het gebruik van de ITT en de gecombineerde GHRH met arginine test bij oudere patiënten laten verschillende uitkomsten zien. Sommige studies geven aan dat er een lagere GH piek is bij ouderen vergeleken met jongere patiënten, terwijl andere studies geen verschil laten zien. Wanneer er helemaal geen rekening wordt gehouden met leeftijd bij het bepalen van de afkapwaarden kan het zijn dat patiënten onterecht gediagnosticeerd worden met GHD. Ondanks deze controversiële uitkomsten moet er toch rekening gehouden worden met leeftijd. In hoeverre dit van invloed is voor het effect van rhGH therapie bij deze patiëntengroep is nog onduidelijk.

De afname van de GH concentratie gaat gepaard met een daling van de IGF-I concentraties. IGF-I SD scores worden gebruikt voor de diagnose van GHD, maar ook voor het goed instellen van de rhGH behandeling. Het is dus ook noodzakelijk voor leeftijd gecorrigeerde IGF-I SD scores te bepalen. Vanuit een evolutionair perspectief blijkt de natuurlijke daling van GH en IGF-I tijdens veroudering zelfs gunstig. In onderzoek met dieren blijkt dat een verminderde GH-IGF-I functie de levensduur van de dieren verlengd. In hoeverre dit van toepassing is bij de mens is nog niet duidelijk. Maar een klein aantal studies laat een gunstig effect zien van rhGH bij oudere patiënten. De vraag blijft dus of de behandeling van ouderen met rhGH klinisch relevant is. Er is meer onderzoek nodig in deze patiënten groep om dit goed te kunnen beoordelen.

V. Slotopmerkingen

Hypofyse functie na TBI

Er is een grote variatie in gerapporteerde prevalentie cijfers van hypopituïtarisme na traumatisch hersenletsel. Dit wordt voor een deel veroorzaakt door het gebruik van verschillende endocriene testen, verschillende afkapwaarden en het niet rekening houden met overige factoren die van invloed (kunnen) zijn (zoals BMI). Door deze methodologische verschillen is het niet mogelijk de uitkomsten van deze verschillende studies met elkaar te vergelijken.

Wanneer juiste endocriene testen en strenge criteria worden gebruikt is de prevalentie van hypopituïtarisme na een traumatisch hersenletsel waarschijnlijk zeer laag. De gerapporteerde prevalentie van hypofyse insufficiëntie na een traumatisch hersenletsel is zeer waarschijnlijk overschat.

Hypofyse functie na transsfenoïdale chirurgie

De CRH test lijkt een waardevolle aanvulling in het diagnostisch arsenaal van endocrinologische testen om klinisch relevant cortisol tekort te definiëren onmiddellijk na hypofyse chirurgie. Deze test is weinig belastend en kan veilig worden gebruikt om te beslissen of patiënten met of zonder hydrocortison uit het ziekenhuis worden ontslagen. Gedurende follow-up is het echter wel noodzakelijk de HPA as nogmaals te testen.

De prevalentie van bijnierinsufficiëntie bij patiënten in remissie van acromegalie na TS is zeer laag (9%) een jaar na operatie. Het optreden van ‘late-onset’ bijnierinsufficiëntie is een zeer zeldzame complicatie bij patiënten met acromegalie in remissie na transsfenoidale chirurgie.

Hypofyse functie na craniële radiotherapie

Hypopituïtarisme is een veelvoorkomende complicatie bij volwassenen na craniële radiotherapie voor niet-hypofysaire tumoren. Daarom moeten alle patiënten die worden behandeld met craniële radiotherapie tijdens follow-up een gestructureerde periodieke beoordeling van de hypofyse functies ondergaan. Dit moet worden opgenomen in richtlijnen voor de behandeling en follow-up van deze patiënten.

Hypofyse functie bij ouderen

RhGH therapie bij oudere patiënten met GHD verlaagt het LDL-cholesterol gehalte en verbetert de kwaliteit van leven, maar de overige effecten zijn niet eenduidig. Er zijn geen gegevens over de werkzaamheid en veiligheid van rhGH behandeling in tachtigjarige patiënten met GHD. Er zijn tot slot ook geen gegevens bij oudere patiënten met GHD over klinisch relevante eindpunten zoals cardiovasculaire aandoeningen of breuken. Gezien de hoge kosten van de behandeling en de potentiële schadelijke effecten van suprafysiologische rhGH substitutie op het ontstaan van maligniteiten adviseren we gerandomiseerd onderzoek bij de oudere patiënt met GHD met een weloverwogen lange termijn kosten-baten analyse.

Curriculum Vitae

Nieke Eva Kokshoorn werd geboren op 4 december 1982 te Voorburg. Zij behaalde in 1999 eerst haar HAVO diploma gevolgd door haar VWO diploma in 2001. Beide aan het Veurs College te Leidschendam. Aangezien ze het vak Scheikunde miste om mee te mogen loten voor de opleiding Geneeskunde heeft ze deze in 2001 behaald bij het Kades College te Den Haag. Ze werd ingeloot voor de opleiding Geneeskunde aan de Universiteit van Maastricht. Na zes mooie jaren in Maastricht te hebben doorgebracht heeft zij in 2008 haar artsenbeul behaald. In september 2008 startte zij als promovenda bij de afdeling Endocrinologie van het Leids Universitair Medisch Centrum onder leiding van Prof. dr. J.A. Romijn, Prof. dr. J.W.A. Smit en Dr. A.M. Pereira. De resultaten van haar promotieonderzoek staan beschreven in dit proefschrift.

List of publications

1. **Kokshoorn NE**, Wassenaar MJ, Biermasz NR, Roelfsema F, Smit JW, Romijn JA, Pereira AM. Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values. Eur J Endocrinol. 2010 Jan;162(1):11-8. Epub 2009 Sep 25. Review.

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3. **Kokshoorn NE**, Biermasz NR, Roelfsema F, Smit JW, Pereira AM, Romijn JA. GH replacement therapy in elderly GH-deficient patients: a systematic review. Eur J Endocrinol. 2011 May;164(5):657-65. Epub 2011 Feb 21. Review.

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5. **Kokshoorn NE**, Appelman-Dijkstra NM, Dekkers OM, Neelis KJ, Biermasz NR, Romijn JA, Smit JW, Pereira AM. Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Aug;96(8):2330-40. Epub 2011 May 25.

6. **Kokshoorn NE**, Smit JW, Nieuwlaat WA, Tiemensma J, Bisschop PH, Groote Veldman R, Roelfsema F, Franken AA, Wassenaar MJ, Biermasz NR, Romijn JA, Pereira AM. Low prevalence of hypopituitarism after traumatic brain injury: a multicenter study. Eur J Endocrinol. 2011 Aug;165(2):225-31. Epub 2011 Jun 6.

7. **Kokshoorn NE**, Romijn JA, Roelfsema F, Rambach AHJH, Smit JWA, Biermasz NR, Pereira AM. The use of an early postoperative CRH test to assess adrenal function after transsphenoidal surgery for pituitary adenomas. Pituitary. 2011 Sep 9. [Epub ahead of print].

Notes