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Hypopituitarism after Surgical Adenomectomy in Adult Patients with Acromegaly – A Review with Emphasis on Growth Hormone Deficiency

Yuh-Min Song[1,2]

[1]Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation;
[2]School of Medicine, Tzu Chi University, Hualien, Taiwan

Abstract

Excessive secretion of growth hormone (GH) from a pituitary adenoma and the consequent increase in synthesis and secretion of insulin-like-growth factor-1 (IGF-1) from the liver causes acromegaly. Aggressive treatment is usually required for this disorder, especially for large tumors, with aims to remove the mass lesions as much as possible and correct hormonal abnormalities. In addition to the better known hypopituitarism affecting the pituitary-adrenal, -thyroid, and/or -gonadal axes, a rare but clinically significant outcome of treatment is a deficiency of GH. In the long run, this may result in a decrease in lean muscle mass, fat accumulation, and increases in the incidence of metabolic syndrome and diabetes, thereby increasing morbidity and mortality in this patient population. Poor quality of life is another dominant feature of a lack of GH. Although there is still controversy about the long term benefits for health maintenance and mortality after GH replacement, a close look into the potential benefits of replacement therapy in correction of the multiple abnormalities caused by GH and IGF-1 deficiencies is still warranted. This literature review was undertaken to raise clinical attention and concern about the recognition, diagnosis, and treatment of various forms of hypopituitarism after surgery on the pituitary gland, with emphasis on GH deficiency. (J Intern Med Taiwan 2018; 29: 230-239)

Key Words: Acromegaly, Adult, Growth hormone deficiency, rhGH replacement

Introduction to the Management of Patients with Acromegaly

One of the major hypersecreting adenomas of the pituitary gland is growth-hormone (GH)-secreting adenoma. This leads to a clinical picture of acromegaly in adults, or gigantism when oversecretion of GH develops prior to or during development in adolescence before closure of the growth plates of the long bones. Untamed oversecretion of both GH and the accompanying effector insulin-like growth factor-1 (IGF-1) leads to disorders of multiple organs. This is not limited to the skeletal and muscular systems with changes in physical features, but also results in significantly higher morbidity and mortality due to development of multiple cardiovascular risk factors in these patients compared with the general

Reprint requests and correspondence：Dr. Yuh-Min Song
Address：Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 88, Sec. 1, Fengxing Rd., Tanzi Dist., Taichung City 427, Taiwan (R.O.C.)

population[1-4]. The mainstay of treatment is surgical removal of the offending adenoma. Surgery is mostly successful with microadenomas (tumors less than one centimeter at the greatest diameter) and in the hands of experienced surgeons. However, in resistant cases such as with macroadenomas (greater than one centimeter in diameter) or mass lesions invading surrounding structures (especially vascular encroachment) leading to difficulty in the surgical approach, control of persistently higher-than-normal GH and/or IGF-1 levels is required. This is done with modalities including dopamine-agonists, somatostatin analogues, somatostatin-receptor antagonists, and/or gamma-knife radiosurgery to residual lesions, aiming to cure the disorder as much as possible[5,6]. The treatment goals in patients with acromegaly are as follows: (1) removal of the tumor mass (2) restoration of various pituitary hormones to within the normal ranges, and (3) avoiding hypofunctioning of the various pituitary and target endocrine organs after treatment. When a biochemical cure is achieved, clinicians must also pay attention to various pituitary hormonal functions, including a possible deficiency in GH, all of which may individually or together lead to derangement of multiple physiological functions and even an increase in mortality[7].

Hypopituitarism after surgery on the pituitary gland

With the aggressiveness of both the original tumor mass as well as the treatment modalities applied to these lesions, the risk of developing hypofunction of pituitary hormones is high[8-12]. Most notably, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) deficiencies require immediate diagnosis and supplementation, since depletion of the respective target hormones, namely cortisol and thyroid hormones, can develop rapidly and is detrimental to the general health of the patient. The signs and symptoms and laboratory confirmation of these disorders are not easily missed by a cautious clinician and patients can usually receive adequate management of these hormonal deficiencies without difficulty.

After surgery on the pituitary gland, clinical suspicion of and evaluation for possible hypoadrenalism are needed when there is euvolemic hyponatremia or unexplained hypotension. Central hypoadrenalism does not cause hyperkalemia as in primary adrenal insufficiency since the renin-angiotensin-aldosterone axis between the renal system and the intact zona glomerulosa of the adrenal cortex plays a dominant role in maintaining potassium homeostasis, so replacement with mineralocorticoids is usually not required. In a well-designed prospective study of 139 consecutive patients who underwent surgery for pituitary adenoma or Rathke cleft cyst, glucocorticoids (GC) were withheld in patients with normal preoperative levels of cortisol and ACTH who had morning cortisol levels higher than 4 μg/dL (110 nmol/L) on postoperative days 1 and 2. During a mean follow-up time of 10 months, some of these patients could be weaned from the supplements depending on clinical and biochemical evaluations. Five of the 139 patients (3.6%) needed long-term GC replacement therapy. There was a positive predictive value of 98% using this cutoff level[13]. When indicated, the dose of GC depends on the clinical scenario. During an acute illness, an intravenous loading dose of 100 mg hydrocortisone is administered, followed by 50 mg hydrocortisone every 6 hours intravenously (or a total daily dose of 200 mg by continuous infusion), which can be tapered gradually according to the clinical status[14]. For maintenance therapy, oral hydrocortisone 15-20 mg is administered in the morning and 5-10 mg in the evening. Some caveats should be considered in supplementing GC. With coexistent hypothyroidism requiring thyroid hormone replacement, it is critical to administer GC well before the thyroid tablet to prevent an adrenal crisis precipitated by the rising

thyroid hormone concentration with accelerated turnover of any form of GC[15]. In patients with GH deficiency, recombinant human GH (rhGH) replacement raises the IGF-1 concentration, which has the potential to inhibit 11-β-hydroxysteroid dehydrogenase type 1, an enzyme that plays a role in the regeneration of cortisol from the liver and adipose tissue in peripheral cortisol metabolism[16,17]. Hence, an increase in the dose of GC may be required with long-term rhGH administration. A higher dose of GC may also be required in women on oral estrogen replacement therapy since estrogen can raise the concentration of cortisol binding globulin. This effect has not been observed when estrogen is given via the transdermal route[18].

In patients with euthyroidism on preoperative pituitary-thyroid axis evaluation, assessment of thyroid function can wait until 4-6 weeks after pituitary surgery since the half-life of circulating thyroxine is about one week. When low free thyroxine (FT4) and/or TSH are repeatedly confirmed, levothyroxine replacement can be commenced and the dose is titrated according to the FT4 level. An optimal therapeutic target for FT4 level is the mid- to upper half of the normal reference range, which can be achieved with a daily dose of 1.6 μg/kg. Measurement of the serum TSH level measurement is not required for follow-up evaluation[19].

Hypogonadism may precede surgery on the pituitary due to either mass effect or cosecretion of prolactin in acromegaly. In an analysis of patients with acromegaly, (54% female), hypogonadism, defined as amenorrhea in women and testosterone deficiency in men, was present in 59% of patients younger than 50 years. Hyperprolactinemia was present in 45% of those with hypogonadism[20]. In another long-term follow-up assessment, hypogonadism, defined by an anovulatory cycle and low follicular-stimulating hormone (FSH) /luteinizing hormone (LH) /estradiol (E2) levels, was found in nearly 70% of acromegalic females between 17 and 45 years old. The causes could be attributed to hyperprolactinemia, tumor mass effect, a direct GH/IGF-1 effect on ovarian function (in cases where no mass effect or hyperprolactinemia was identified and eugonadism returned after correction of high GH/IGF-1 levels), or mixed etiologies[21]. After surgery on the pituitary gland, the patient may recover spontaneously from hypogonadism, as in other hormonal axes, thanks to relief of the underlying pathologies. However, some may still have persistent or newly-developed hypogonadism after treatment[22,23]. The diagnosis of hypogonadism in females derives from clinical symptoms of oligomenorrhea or amenorrhea in premenopausal women with low serum E2 as well as low FSH and LH concentrations. In postmenopausal women, the absence of high serum levels of FSH and LH is sufficient for diagnosis. In male patients, decreased libido, erectile dysfunction, decreased frequency of morning erection, increased visceral fat or development of obesity, fatigue, loss of energy, and/or depression or decreased mood all point to hypogonadism. This should be confirmed by checking the serum total testosterone before 10 AM after an overnight fast, along with measurement of FSH and LH levels. In cases of equivocally low total testosterone levels, free testosterone levels should be determined[24,25]. When hypogonadism is diagnosed, hormone replacement therapy (HRT) is recommended in premenopausal women, provided no contraindications exist. Although there is a reduced risk of bone fractures, critical evaluation of evidence from clinical studies on the benefits and harm of HRT in postmenopausal women has led the US Preventive Services Task Forces to recommend against routine use of combined estrogen and progestin in women with an intact uterus or estrogen alone in hysterectomized women based on findings of increased risks of invasive breast cancer, venous thromboembolism, coronary heart disease, stroke, and dementia[26]. In addition to the clinical signs/symptoms mentioned earlier, androgen deficiency

in males has been linked to the development of metabolic syndrome, which increases the risk of cardiovascular diseases[27]. Testosterone replacement therapy in hypogonadal male patients has been found to not only improve anemia, bone mineral density, libido, sexual function, energy levels, and a sense of well-being, but also reduce fat mass, and increase muscle mass and strength[28]. The reduced fat mass coupled with increased muscle mass is considered a potential mechanism leading to improved insulin sensitivity and glycemic control in diabetes patients. Although there is controversy about the benefits and harm of testosterone replacement therapy in cardiovascular diseases[29-33], endocrine societies currently endorse administration of testosterone to symptomatic males without the following contra-indications: male breast or prostate cancer, with a palpable prostate nodule or induration, a prostate-specific antigen (PSA) level > 4.0 ng/mL (or > 3.0 ng/mL with a high risk of prostate cancer), elevated hematocrit (> 48% or > 50% for men living at high altitude), untreated obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia. In men older than 65 years who meet the diagnostic criteria for hypogonadism, testosterone therapy can be offered after individualized discussion of the risks and benefits. The goal for the testosterone level should be set at the mid-normal range for healthy young men with planned follow-up of testosterone levels and the hematocrit at 3, 6, and 12 months in the first year of treatment and then annually. It is also essential to measure the PSA level between 3 and 12 months after initiation of therapy[34].

Another rare hormonal deficiency after treatment in an acromegalic patient is, ironically enough, depletion of GH synthesis and secretion, which is in fact the primary target of treatment from the outset. According to a retrospective study carried out in a referral center in the UK investigating the impact of hypopituitarism on life expectancy, 76% (131 of 172) of adult patients diagnosed with partial or complete hypopituitarism had primary lesions in the pituitary gland. Nonfunctional tumors comprised most of the lesions (120/131), and most of these patients had received surgical treatment and/or radiotherapy. The primary causes in the remaining 24% of patients were identified as extrapituitary tumors, followed by idiopathic causes, basal sarcoid, trauma, and Sheehan's syndrome. A total of 98 of the 172 (57%) patients received insulin stress tests and 94/98 (96%) were diagnosed with GH deficiency, defined as a peak GH level less than 5 mU/L[35]. GH deficiency, whether iatrogenic or not, has negative impacts on the functions of multiple organs and leads to metabolic derangement including obesity, dyslipidemia, diabetes mellitus, cardiovascular disorders, and shorter life span compared to people with normal GH reserve[36-38]. Despite the lack of universal consensus or applicable guidelines in different regions and countries, clinicians must be alert to the recognition, correct diagnostic workup, and adequate supplementation therapy and follow-up when facing these rare clinical scenarios[39-42].

Diagnosis of GH Deficiency

The correct diagnosis and adequate treatment of any clinical disorder starts with clinical suspicion. In patients with acromegaly, GH deficiency after treatment can be predicted from the number of hormonal deficiencies in other pituitary-target organ axes. Most GH deficiency is found in those with three or more such deficiencies[43,44]. This is likely caused by the more severe destructive processes applied onto a large and/or difficult-to-approach tumor mass in initial treatment[45]. A large pituitary tumor may also be a cause of GH deficiency even before any treatment procedure is applied, a condition found in studies investigating non-functioning pituitary tumors[46].

After other possible hormonal deficiencies

ranging from hypothyroidism to adrenal insufficiency and/or hypogonadism have been diagnosed and adequately corrected, the clinical picture that may raise diagnostic alertness of GH deficiency includes generalized lethargy, central obesity, pale face, and fine wrinkles on face, which are noted to develop only after acromegaly has been treated.

When GH deficiency is suspected, laboratory tests are warranted before treatment is started[47,48]. A normal IGF-1 level alone may not be accurate enough to exclude GH deficiency, but when the IGF-1 level is lower than the age- and sex-matched normal ranges and especially when there is co-existent evidence of deficiencies of 3 or more pituitary-end-organ axes, a diagnosis of GH deficiency is established without a need for further affirmative tests[49]. Measurement of only the baseline GH may not be reliable for a definitive diagnosis because of the dynamic secretion pattern of the hormone. A stimulation test is thus usually required. The insulin tolerance test (ITT) and growth hormone-releasing hormone (GHRH) + arginine test are most commonly recommended in clinical guidelines because they have sufficient sensitivity and specificity to establish a diagnosis of GH deficiency. When GHRH is not available or an ITT is contraindicated or not feasible in frail patients, a glucagon stimulation test can be an alternative[50]. One pitfall in interpreting GH secretion after any of the dynamic tests is noted in cases of obesity[51]. Corneli et al[52] studied GH secretion after the GHRH + arginine stimulation test in patients with various pituitary hormone deficiencies caused by hypothalamic-pituitary organic disorders. They found that the cutoff value for the stimulated peak GH level differed significantly according to the body mass index (BMI) as follows: 4.2 ug/L in obese subjects (BMI $\geqq$ 30 kg/m^2), 8.0 ug/L in overweight subjects (BMI $\geqq$ 25 and < 30 kg/m^2), and 11.5 ug/L in lean subjects (BMI < 25 kg/m^2). (Figure) GH levels in obese subjects have been found to be lower for several physiological reasons, including decreased

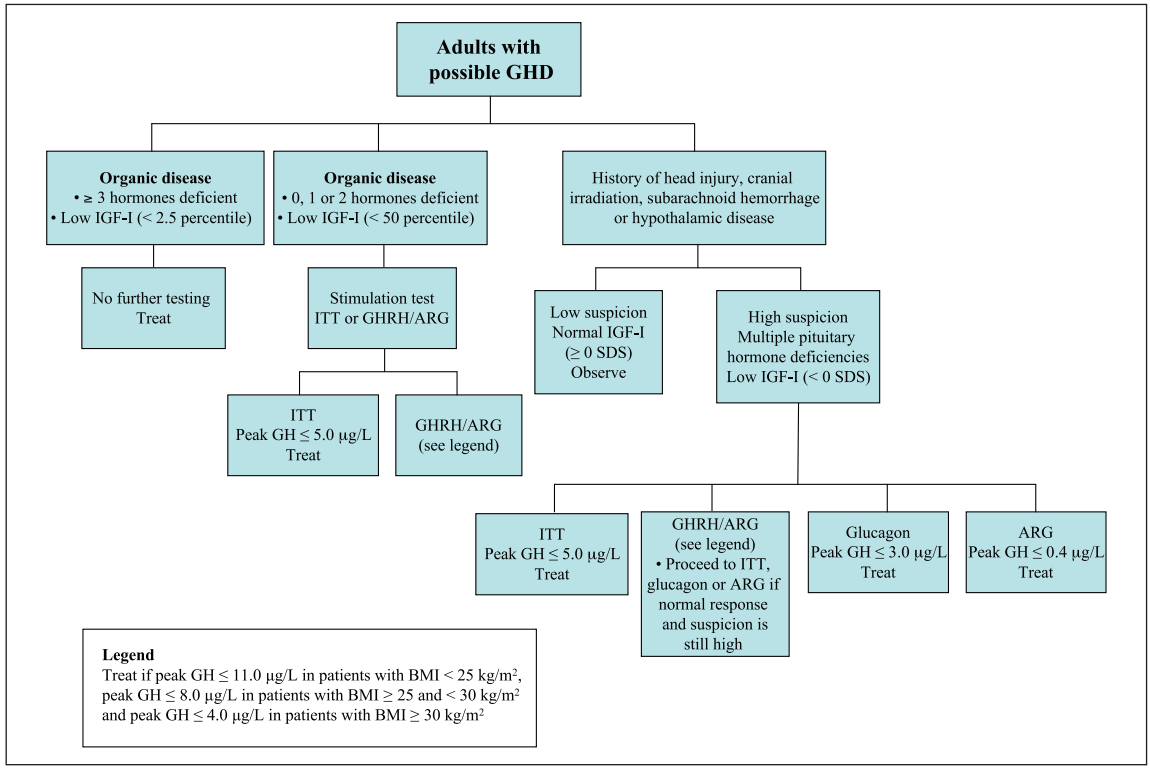

Figure. Tests for growth hormone stimulation. Cook et al. [49].

synthesis and secretion in patients with persistently elevated free fatty acids and hyperinsulinemia, as well as a reduced half-life[53-55].

One agent that has been recently approved by the US FDA for the diagnosis of GH deficiency in adults is a ghrelin mimetic (macimorelin). Use of this drug is convenient because it is given orally[56]. In a validation study carried out in adults with GH deficiency versus controls, this oral test was found to have discrimination comparable to the GHRH + arginine test. The peak stimulated GH was also noted to have an inverse association with BMI in control subjects with obesity (BMI > 30 kg/m^2), a finding not different from previous conclusions. This test can be completed within 90 minutes.

Treatment of GH Deficiency with rhGH Replacement

When GH deficiency is confirmed after a dynamic test of GH secretion as well as lower-than-normal IGF-1 levels, treatment with GH supplementation can be started since spontaneous recovery from GH deficiency is less likely than with deficiencies of other pituitary hormones such as gonadotropins, ACTH, and TSH[57]. Although there is controversy about the long-term benefits of GH supplementation, this treatment can correct multiple disorders brought about by GH deficiency, including improvement in several cardiovascular surrogate outcomes, such as endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness, and aspects of myocardial function, as well as quality of life[58,59]. The recommended starting dose of rhGH is low at 2-5 ug/kg/day subcutaneously once daily[60]. This low starting dose may avoid possible side effects, such as peripheral edema, arthralgia, carpal tunnel syndrome, paresthesias, and a possible worsening of glucose tolerance due to the antagonizing effect of high GH concentrations against insulin.

Synergistic Effects of GH and Testosterone Replacement Therapy

Some clinical features that can raise the risk of cardiovascular diseases are seen in both GH deficiency and hypogonadism, such as increased visceral adipose tissue, proatherosclerotic lipid profiles, and inflammatory markers including high-sensitive C-reactive protein and proinflammatory cytokines[61-65]. A therapeutic strategy is required to address all these risk factors when these disorders coexist.

In studies of men with hypopituitarism, coadministration of GH and testosterone enhanced the resting energy expenditure, fat oxidation, and stimulated synthesis of protein to a greater extent than either treatment alone, indicating an additive effect of these two anabolic hormones. Furthermore, the anabolic effect of testosterone administration on protein synthesis through reducing protein breakdown and oxidation was only seen in the presence of GH replacement[66,67]. On the other hand, hypogonadism, in both females and males can affect the therapeutic effect of GH therapy in stimulating IGF-1 synthesis. After correction of sex hormone deficiency in hypogonadal subjects, the response to GHRH stimulation or IGF-1 synthesis is enhanced. As a consequence, when both GH deficiency and hypogonadism are present, adequate treatment of hypogonadism is essential to the success of GH replacement therapy[68].

Goals and Maintenance of rhGH Replacement Therapy

The goal for the IGF-1 level is at the middle of the age- and sex-matched ranges[58]. When this goal is not obtained after two months of therapy, the daily dose is titrated up by 1-2 ug/kg at two-month intervals. In female patients on oral estrogen therapy, the starting dose is toward the higher end of the range since the hepatic response of IGF-1 synthesis

in hepatocytes to GH stimulation is not as sensitive in those on oral estrogen compared to those using transdermal estrogen or a placebo. An increase in IGF-I clearance has been postulated as another possible mechanism[69]. Patients with morbid obesity may also require a higher dose of rhGH to effectively raise IGF-1 levels[52,70]. The treatment effect is best monitored by measurement of IGF-1 levels. After the optimum level is reached, follow-up is recommended every 6-12 months for possible dose adjustment.

Safety Issues for Tumor Growth with rhGH Administration

The potential for stimulating tumor growth has been a concern in rhGH replacement therapy. In a nation-wide surveillance of adults with severe GH deficiency in Holland (1998 to 2009), rhGH therapy did not seem to increase the rate of recurrence of pituitary adenoma[71].

How Long Should rhGH Be Given?

There is no consensus on the duration of therapy. A cohort study of 64 patients who had discontinued rhGH for more than 12 months in Denmark[72] showed some benefits of rhGH replacement therapy could be observed in patients younger than 60 years old. Besides an increase in body fat mass and a significant decrease in bone turnover markers within the first 12 months after discontinuation of therapy in patients older or younger than 60 years, there were no other obvious metabolic derangements after three years of follow-up. However, there were small but significant decreases in BMI and bone mineral density in the femoral neck in patients younger than 60 years. An increase in fat mass concurrent with a decrease in BMI may indicate a decrease in lean body mass after discontinuation of rhGH replacement in this age group. In an additional systemic review of 8 studies, the same authors could not draw a definite conclusion on the benefits or harm of discontinuation of therapy due to inconsistencies in study designs. Further well-designed research is thus required to conclude whether administration of rhGH in adults with GH deficiency should be life-long.

Conclusion

GH deficiency after aggressive treatment of a pituitary adenoma in patients with acromegaly is not commonly encountered and is thus an under-recognized clinical disorder. Previous investigations found that GH deficiency results in the development of multiple cardiometabolic risk factors and increased morbidities and mortality, and there is also clear evidence indicating the benefits of rhGH replacement therapy in restoring health and improving quality of life. A close look into understanding this rare disorder is warranted to help physicians recognize this disorder early, obtain the correct diagnosis, and plan adequate treatment.

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肢端肥大症術後之腦下垂體荷爾蒙缺乏－著重論述生長激素缺乏之文獻回顧

宋育民

台中慈濟醫院　內分泌新陳代謝科

摘　要

因腦下垂體腺瘤過度分泌生長激素引起之肢端肥大症，絕大部分之病患需要以手術方式摘除腺瘤，但往往仍需輔以各類其他療法，才能將生長激素及類胰島素生長因子-1盡量控制在正常範圍，以緩解臨床症狀。然而，除了較被熟知的中樞型腎上腺低下症、甲狀腺低下症，及性腺低下症，有少數病患在術後產生生長激素缺乏的狀況，諸多心血管疾病之風險因子因而產生，如脂肪堆積，骨骼肌減少，代謝症候群，糖尿病，骨密度下降。統計顯示，這些疾患都增加了病患的患病率及死亡率；另外，在前瞻性的臨床實驗中，已證實生長激素製劑的補充療法，已可有意義的緩解前述病症之嚴重程度，此少見疾病之診斷及療法因此值得做一探討。