

## **Brain Injury and Pituitary Dysfunction**

Lisa B. Nachtigall, M.D.

It has been known for over 80 years that brain injury may be associated with hypopituitarism, but recent evidence shows an even higher prevalence of anterior pituitary deficiencies than previously thought. A summary of the recent data on the prevalence of anterior pituitary deficiencies in sub-arachnoid hemorrhage (SAH) and traumatic brain injury (TBI) survivors including the incidence of specific hormonal deficiencies reported is shown in Table 1.

### **Prevalence of Posttraumatic Posterior Pituitary Hormone Deficiencies**

Disorders of water balance are well recognized after TBI, but there are limited reliable data on their true prevalence in post-TBI patients. In one study of 102 patients, 21.6% developed diabetes insipidus (DI) in the immediate post-TBI period and permanent DI remained in 7% of patients (1). In the acute post-TBI period, 13 patients (12.9%) had syndrome of inappropriate secretion of antidiuretic hormone, which persisted in one patient, and one other patient developed cerebral salt wasting (1). Identification of patients with water imbalance is important because appropriate treatment may reduce morbidity and optimize the potential for recovery.

**"There is increasing evidence that pituitary hormone deficiencies occur following traumatic brain injury or subarachnoid hemorrhage."**

### **Prevalence of Posttraumatic Anterior Pituitary Hormone Deficiencies**

In short-term studies, approximately 35% of patients have at least one deficiency within three months of the initial injury (2-4). Long-term survivors of both TBI and aneurysmal SAH have been found to have a 30–55% prevalence of at least one anterior pituitary deficiency when evaluated up to six years after the initial injury (5-8). The prevalence of anterior pituitary dysfunction was even higher in one study of TBI survivors when neuroendocrine testing was performed more acutely (7 to 20 days after the trauma) in which 80% of subjects had gonadotropin deficiency (4). However, in this study hyperprolactinemia was present in half the subjects, which could have been the result of medications or seizures complicating the acute phase of injury. Thus, hyperprolactinemia may have caused the high rate of gonadotropin deficiency unique to this study of hormonal changes within three weeks of injury.

The type of brain injury may relate to the frequency and type of pituitary hormone deficiencies. Given that corticotropes are thought to be more resistant to injury than gonadotrophs and somatrotrophs, it is surprising that a long-term study in SAH patients shows a higher incidence of central adrenal insufficiency (40%) and a lower incidence of central hypogonadism than in studies comprised predominantly of TBI patients (6). Potential confounding variables include age and gender. The SAH group contains mostly women who were older, while the TBI subjects were mostly male and significantly younger on average. In addition, different methods of dynamic testing were used. Finally, the long-term SAH did not specifically cite exogenous glucocorticoid use as exclusion criterion, although authors mention that a history of steroid use was not documented in the majority of cases. Interestingly, a short-term study which evaluated a similar group of older women at three months after the initial hemorrhage, had opposite findings, with a very low prevalence of adrenal insufficiency (3%) (3). This suggests that it may be important to evaluate patients beyond the initial three months, as hypoadrenalism may not become apparent until later. More consistent findings were reported in several recent studies regarding growth hormone deficiency and central hypothyroidism, which occurred in approximately 25% and 5% of brain injured subjects respectively (2-8).

### **Risk Factors for Hypopituitarism in Patients with Brain Injury**

The risk factors for developing hypopituitarism after cerebral injury have not been determined. Several short-term studies suggest that severity of injury correlates with a higher rate of loss of anterior pituitary function within three months of the event (2,4). With a single exception (5), the long-term studies showed no correlation between loss of pituitary function and severity of brain injury, edema or anatomic findings on brain imaging (6-8). The discrepancy among results raises the question as to when testing of hormone deficiencies should be conducted. Since longitudinal observations from prospective studies have not yet been reported, the timing of onset and the duration of specific anterior pituitary deficiencies have not been determined. In a review by Benvenga, it was clear that in the majority of TBI cases, pituitary deficiencies were discovered within the first year after the trauma (9). However, in about 5% of patients with posttraumatic hypopituitarism, there was an over 20-year lag period between injury and diagnosis (9). Individual studies vary in the number and selection criteria of subjects and the methods of dynamic pituitary testing, possibly accounting for the differences in specific patterns of pituitary deficiencies reported. Prospective studies will be necessary to establish the timing of hormone loss after brain injury.

### Pathophysiology of Hypopituitarism after Brain injury

The pathophysiology of pituitary deficiencies following brain injury has not yet been elucidated. Hypoxic or hypotensive crises and/or raised intracranial pressure causing hypothalamic damage could be postulated, but these hypotheses have not been systematically studied and it is unknown whether the deficiencies identified are hypothalamic or pituitary in origin. In autopsy studies of patients who died due to TBI, there is an up to 50% incidence of hemorrhage in the pituitary capsule and up to 30% incidence of either necrosis of the anterior pituitary or stalk hemorrhage (9). However, the autopsy studies include the most severe cases, those who died from the acute trauma, and may not reflect the pathophysiology of long-term pituitary failure in survivors.

<b>Table I.</b> <b>Hypopituitarism</b> <b>After Brain</b> <b>Injury: Summary</b> <b>of Recent</b> <b>Reports</b> Author/year	Number of Subjects (male/female)	Age of subjects (mean years)	TBI or SAH	Time since injury (mean months)	% At least 1 pituitary hormone deficiency	AI %	GHD %	HH %	CH %
*Kelly 2000 (2)	26 (18/6)	28	both	3	37	4	29	17	4
Aimaretti 2004 (3)	100 (69/31)	37	TBI	3	35	8	25	4	5
Aimaretti 2004 (3)	40 (14/26)	51	SAH	3	38	3	25	13	8
*Agha 2004 (4)	50 (38/12)	37	TBI	0.5	80	16	18	80†	2
Lieberman 2001(8)	70 (46/24)	32	both	49	54	7	15	3	11
Agha 2004 (7)	102 (85/17)	28	TBI	17	28	23	18	12	7
Kreitschmann- (6) Andermahr 2004	40 (14/26)	44	SAH	27	55	40	20	0	3
*Bondanelli 2004 (5)	50 (40/10)	38	TBI	12 – 64 (range)	54	0	28	14	10

AI = adrenal insufficiency GHD = growth hormone deficiency HH = hypogonadotropic hypogonadism CH = central hypothyroidism \*indicates significant correlation between severity of injury and prevalence of pituitary hormone deficiency SAH = subarachnoid hemorrhage, TBI = traumatic brain injury both = subjects with SAH and TBI were included  
† = this includes 50% of patients that had hyperprolactinemia as possible cause of HH

While the etiology of the pituitary dysfunction is unknown, these hormonal deficiencies may have significant impact on quality of life. Fatigue, cognitive dysfunction and depression are known to limit rehabilitative progress and quality of life in these patients. Such symptoms could potentially stem from or be compounded by a treatable, unrecognized pituitary hormone deficiency (10-12). Furthermore, cardiovascular disease has been found to be the most important cause of death in long-term SAH survivors and an excessive mortality from cardiovascular disease has been reported in patients with hypopituitarism (13). Thus, hypopituitarism is a potential factor contributing to the excess cardiovascular mortality in brain injury survivors. Unrecognized adrenal insufficiency is also a potential cause of morbidity and of mortality if adrenal crisis occurs.

### **Neuroendocrine Testing**

Given the published data currently available, it is reasonable to suggest routine neuroendocrine testing for survivors of brain injury. Which tests to perform and when to perform them in a cost effective and practical manner has not been formally examined. Using general principles of neuroendocrine testing for hypopituitarism, initial evaluation might include assessment of serum free T4, TSH, AM cortisol, prolactin, IGF-1, testosterone (in men) and FSH (in postmenopausal and/or premenopausal women with amenorrhea). If the AM cortisol is less than 3 ug/dl, the diagnosis of adrenal insufficiency is established. If the AM cortisol is greater than 18 ug/dl, then adrenal insufficiency is excluded in most patients. Levels of serum AM cortisol between 3 ug/dl and 18 ug/dl warrant a cortrosyn stimulation test, which should be done at least 6-12 weeks after the initial injury, as earlier testing may yield false negative results for central adrenal insufficiency. Low gonadotropins in the setting of amenorrhea or low testosterone suggest hypogonadotropic hypogonadism and a structural lesion should be excluded. Hyperprolactinemia should also be considered as a cause of hypogonadism because in some cases normalization of prolactin (via medication changes or administration of a dopamine agonist) could reverse hypogonadism. A low IGF 1 with other pituitary deficiencies has a high probability of representing growth hormone deficiency. If the IGF-1 is normal, or low in the absence of other pituitary deficiencies, dynamic testing for growth hormone deficiency is appropriate if the patient is a candidate for growth hormone replacement. Insulin tolerance testing should be avoided in those patients with neurologic abnormalities who may be at risk for seizure. A less hazardous test for growth hormone deficiency is the Arginine/GHRH stimulation test although hypothalamic causes of growth hormone deficiency could be missed by this test (14).

### **Summary**

In summary, there is increasing evidence that pituitary hormone deficiencies occur following traumatic brain injury or subarachnoid hemorrhage. Testing for pituitary deficiencies is appropriate in all patients with a history of TBI or SAH within the first 6-12 months of the event. If there are signs or symptoms suggestive of inadequate adrenal, sex steroid, growth hormone or thyroid function, pituitary testing should be done sooner. Longitudinal follow-up is necessary, as not all patients sustain permanent deficiencies and some develop hypopituitarism as a late manifestation many years after the initial event. Prospective studies will help determine the timing at which deficiencies develop, and provide information regarding the benefits derived from hormone replacement during rehabilitation from brain injury.

### **References**

1. Agha A, et al. *J Clin Endocrinol Metab.* 2004; 89:5987-92.
2. Kelly DF, et al. *J Neurosurg.* 2000; 93:74352.
3. Aimaretti G, et al. *Clin Endocrinol (Oxf).* 2004; 61:320-6.
4. Agha A, et al. *Clin Endocrinol (Oxf).* 2004; 60:584-91.
5. Bondanelli M, et al. *J Neurotrauma.* 2004; 685-96.
6. Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab.* 2004; 89:4986-92.
7. Agha A, et al. *J Clin Endocrinol Metab.* 2004; 89:4929-36.
8. Lieberman SA, et al. *J Clin Endocrinol Metab.* 2001; 86:2752-6.
9. Benvenga S, et al. *J Clin Endocrinol Metab.* 2000; 85:1353-61.
10. Van Baalen B, et al. *Disabil Rehabil.* 2003; 25:9-18.

11. Hutter BO, et al. Acta Neurochir Suppl (Wien). 1999; 72:157-74.
  12. Wallymahmed ME, et al. Clin Endocrinol (Oxf). 1999; 51:333-8.
  13. Rosen T, Bengtsson B-A. Lancet. 1990; 336:285-8.
  14. Biller BMK, et al. J Clin Endocrinol Metab. 2002; 87:2067-79.
- 

## **Physiologic Cortisol Dynamics and Cushing's Syndrome in Pregnancy**

Andrea L. Utz, M.D., Ph.D.

Although the occurrence of Cushing's syndrome during pregnancy is rare, correct and expedient diagnosis is imperative due to the high rate of maternal and fetal complications associated with the disorder. Normal pregnancy is accompanied by an increase in cortisol concentration and this may complicate the diagnosis of Cushing's syndrome. Knowledge of normal pregnancy cortisol levels is necessary to separate physiologic from pathologic increases in cortisol.

### **Normal Cortisol Production in Pregnancy**

The progression through pregnancy produces an increase in serum cortisol concentration and a decrease in the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis to exogenous glucocorticoids. High estrogen levels of pregnancy induce an increase in cortisol binding globulin (CBG) and this in turn increases corticotropin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and total cortisol levels to maintain an adequate free cortisol concentration. Additionally, as pregnancy progresses, there is an increase in the free fraction of cortisol and thus an increase in the daily urinary excretion of cortisol. The exact mechanism of the increase in free cortisol is unknown but potential contributors include autonomous production of CRH and/or ACTH by the placenta or a state of glucocorticoid resistance during pregnancy. Normative reference ranges for ACTH and serum and urine cortisol levels during the trimesters of pregnancy do not exist. Based on preliminary studies, an approximate two to three fold increase in these concentrations, compared to the non-pregnant state, is apparent by the second trimester of pregnancy and persists through the early postpartum period. Defining pathologic states of cortisol excess or insufficiency is hindered by a lack of well-defined reference ranges during pregnancy.

### **A Study to Assess the Safety and Efficacy of SOM 230 in Patients with Cushing's Disease**

This clinical research study is designed to investigate the effects of an investigational medication (not approved by the Food and Drug Administration), SOM 230, in patients with active Cushing's disease. Primary treatment for Cushing's disease is surgery to remove the tumor causing elevated ACTH and cortisol levels. SOM 230 may provide an alternative medical treatment for patients with Cushing's disease. All adult subjects who have been diagnosed with Cushing's disease and who have not previously undergone medical and/or radiation therapy for the Cushing's or who have not been cured with surgery may be eligible for this study. There are 9 visits over one month of study participation. Patients will receive a total of \$1000 for completing the study and SOM 230 at no charge. Those patients who receive benefit from this medication will be offered enrollment in an extension study where SOM 230 will be offered at no charge until it is approved by the Food and Drug

## Cushing's Syndrome During Pregnancy

The diagnosis of Cushing's syndrome is rare during pregnancy because elevated cortisol levels often result in

anovulatory menstrual cycles and thus infertility. However, the detrimental results of hypercortisolemia on maternal and fetal well-being underscore the importance of early identification and treatment of Cushing's syndrome in the pregnant patient. Reported fetal complication rates include: prematurity (43%), intrauterine growth retardation (21%), stillbirth/spontaneous abortion/intrauterine demise (11%), and hypoadrenalism (2%). Because pregnancy and Cushing's syndrome share similar clinical signs and symptoms, distinguishing individuals with hypercortisolism can be difficult. For example, both states may be accompanied by hypertension, glucose intolerance, increased weight, striae, and amenorrhea. However, certain clinical indicators should increase the suspicion for Cushing's syndrome, such as hypokalemia, proximal muscle weakness, and ecchymoses.

Administration.

Please contact Karen Liebert, R.N. at 617.726.7473 or [kpulaski@partners.org](mailto:kpulaski@partners.org)

**Table 1. Distribution of Sources of Hypercortisolemia in Pregnant and Non-Pregnant Individuals.**

	Non-pregnant (%)	Pregnant (%)
Pituitary	68	33
Adrenal		
Adenoma	10	46
Carcinoma	8	10
Adrenal hyperplasia	1	3
Ectopic	12	3
Other / undetermined	1	5

*Adapted with permission from Orth et al. New England Journal of Medicine 1995; 332:791-803 and Lindsay et al. Endocrine Reviews 2005; 26:775.*

## Diagnosis

When Cushing's syndrome is suspected in pregnancy, the initial test should be measurement of 24-hour urinary cortisol excretion. Cortisol levels higher than 3-fold the upper limit of the non-pregnant state suggest the diagnosis of Cushing's syndrome. For equivocal results, measurement of midnight salivary cortisol levels may indicate abnormal circadian cortisol dynamics; however, reference ranges for this test have not been established in pregnancy. After hypercortisolemia is determined, the next step is localization of the source. In non-pregnant individuals, the predominant source is a pituitary adenoma. However, in the pregnant woman, an adrenal etiology is more likely (see Table 1). The increase in adrenal etiology may be due to preserved fertility in adrenal versus pituitary Cushing's syndrome. Additionally, rare cases of pregnancy-induced Cushing's syndrome have been documented and can occur as ACTH-dependent and -independent forms. In the ACTH-independent cases, a proposed mechanism is stimulation of illicit receptors on adrenal tissue or adrenal adenomas by substances that circulate in high concentration during pregnancy, such as hCG, LH, or estradiol, with a subsequent increase in cortisol production. These cases do not show abnormalities on pituitary or adrenal imaging and there is prompt resolution of hypercortisolemia following pregnancy.

Measurement of the ACTH level is the next step to distinguish between an adrenal or non-adrenal source of hypercortisolemia. In the absence of exogenous glucocorticoid use, suppressed ACTH suggests an adrenal etiology; however, it should be noted that the normal increase in ACTH during pregnancy may confound interpretation of the ACTH level. In pregnant women with low-normal ACTH levels, 8 mg dexamethasone suppression or CRH stimulation testing may help distinguish an adrenal from a pituitary cause. In a recent report, approximately half of pregnant patients with Cushing's disease suppressed with high-dose dexamethasone, while none of the patients with an adrenal source showed suppression. A positive response to CRH stimulation may also support the diagnosis of Cushing's disease. It should be noted that dexamethasone and CRH are U.S. FDA Pregnancy Category C drugs due to a lack of animal or human studies.

If an adrenal source is suspected, abdominal ultrasound or MRI (without gadolinium contrast) is indicated, avoiding the radiation associated with CT scanning. Alternatively, if the ACTH is normal or elevated, a pituitary MRI should be considered. Risks of MRI in pregnancy have not been fully addressed and therefore the risks of this test must be weighed against the potential benefits of diagnosis. Normal or equivocal findings on the pituitary MRI raise the suspicion for an ectopic ACTH source, although corticotroph adenomas can be too small to visualize on head MRI. In these cases, inferior petrosal sinus sampling procedures, with CRH stimulation, at specialized centers have been performed in pregnant women to confirm the location of ACTH excess. In rare cases of pregnancy-induced Cushing's syndrome, a source may not be detectable with imaging modalities.

## **Treatment**

Due to the significant risks of hypercortisolemia for the mother and the fetus, an expedient plan for cortisol normalization is necessary. In most cases, this entails surgical resection of the hormonally active tumor. Close communication between endocrinologist, surgeon, anesthesiologist and obstetrician is important. Transsphenoidal surgery is the most common approach for resection of a pituitary tumor and adrenalectomy via laparoscopic or open resection can be performed during pregnancy. In cases of adrenal hyperplasia, pregnancy-induced Cushing's syndrome, or to decrease cortisol levels prior to surgical tumor resection, medical therapy may be implemented using adrenal steroidogenesis inhibitors, which are effective in decreasing hypercortisolemia. Although ketoconazole is the first line therapy in the non-pregnant patient, this medication is contraindicated in pregnancy due to risks of teratogenicity. Metyrapone has been shown to be safe and effective for treating hypercortisolism in pregnancy; however it is a U.S. FDA Pregnancy Category C drug due to a lack of animal or human studies. It is no longer commercially available; however, can be obtained from Novartis by calling 1-800-988-7768.

Following definitive treatment of hypercortisolemia with surgery, the patient is often adrenally insufficient, due to preceding suppression of the HPA axis by excess glucocorticoids. Therefore, replacement glucocorticoids are necessary; and in the rare case of bilateral adrenalectomy, mineralocorticoid therapy is also indicated. Hydrocortisone or prednisone are acceptable choices for replacement because the fetus is protected from excess glucocorticoid levels by placental 11- $\beta$ -HSD-2 metabolism of these drugs. However, dexamethasone should be avoided in pregnancy because it is not metabolized by 11- $\beta$ -HSD-2 and thus crosses the placenta. The standard replacement dose required during pregnancy has not been established, but a dose between non-pregnant replacement and double this dose is recommended. Adjustment of dose should be based on clinical signs and symptoms, as there are no accurate laboratory tests to assure adequate glucocorticoid levels. Pregnant women who have been cured of Cushing's should be educated about their adrenal insufficiency status and provided with standard instructions for management during illness. A plan for parenteral glucocorticoid administration is particularly important in the pregnant population. The replacement dose should be doubled for normal vaginal delivery and stress doses provided prior to caesarian section with taper as clinically tolerated to a replacement dose. Glucocorticoid replacement is considered compatible with breastfeeding, with prednisone or hydrocortisone typically used. The dose should be tapered and then discontinued upon HPA axis recovery.

## **Summary**

Normal pregnancy is accompanied by a moderate increase in maternal cortisol levels. In the case of a pregnancy complicated by symptoms of hypercortisolism, the diagnosis of Cushing's syndrome should be systematically pursued. Safe and effective surgical and medical therapies for Cushing's syndrome are available for the pregnant patient and a multidisciplinary approach necessary to improve maternal and fetal outcome in this disorder.

## References

1. Orth DN. N Eng J Med. 1995; 332: 791-803.
2. Lindsay JR, et al. Endocrine Reviews. 2005; 26:775-99.
3. Lindsay JR, et al. J Clin Endocrinol Metab. 2005; 90:3077-83.
4. Hana V, et al. Clin Endocrinol. 2001; 54:277-81.
5. Lacroix A, et al. N Eng J Med. 1999; 341:1577-81.

---

### **SPECIAL LECTURE**

Seventh Annual Nicholas T. Zervas, M.D. Lectureship  
at the Massachusetts General Hospital  
Historic Ether Dome

**Tuesday, May 16, 2006 at 12 Noon**

**“Sleep Loss: A Risk Factor  
for Obesity and Diabetes”**

**Eve Van Cauter, Ph.D.**

Professor, Department of Medicine  
University of Chicago Chicago, IL

For further information call Ivy at 617-726-3870

---

## **Growth Hormone Treatment: Transitioning care from Adolescence to Adulthood** Madhusmita Misra, M.D.

The aim of growth hormone (GH) treatment in childhood has primarily been to optimize growth potential and adult stature in children testing as GH deficient based on GH stimulation tests. Therapy was traditionally stopped when growth velocity decreased to < 1 cm per year, or at a bone age of 15 years in girls or 17 years in boys, when less than 1% of growth potential remained. In the past few years, studies have demonstrated the need for GH replacement in adults with GH deficiency, and have reported improvements in body composition (decreased fat mass and increased muscle mass), increases in bone density, reduction of cardiovascular risk and improvement in quality of life following GH replacement. This raises the issue of lifelong GH therapy and for many children who believed their daily injections would end once adult height was achieved, causes significant disappointment. One question is whether GH treatment may be discontinued for some time in this situation and then restarted without jeopardizing potential beneficial effects of GH replacement. In addition, given that criteria for GH therapy are relatively broad in childhood, it is important to identify truly GH deficient individuals rather than continue GH

replacement in all young adults, some of whom may no longer test as GH deficient. This is particularly important because GH therapy is not without certain side effects; amongst these the risk of developing impaired glucose tolerance and less commonly, frank diabetes. The other important aspect is the tremendous cost of GH replacement.

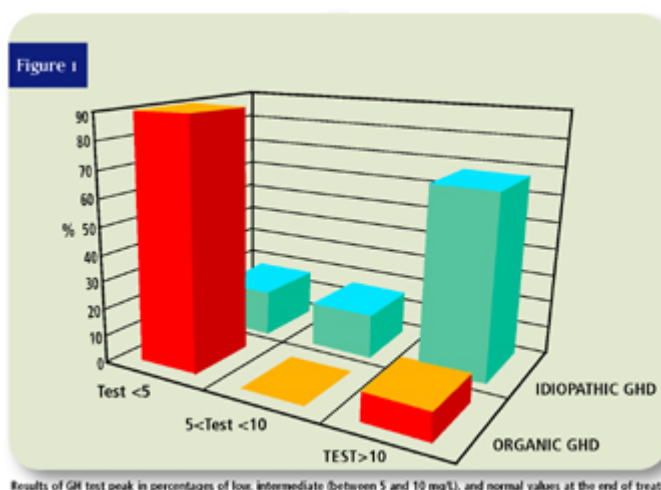
Important considerations at the end of statural growth thus include:

1. Is the individual truly GH deficient based on repeat testing?
2. What is the appropriate dose of recombinant human GH during the transition from childhood to adult replacement?
3. Is a period off GH replacement (GH 'holiday') possible and are there subsequent effects on body composition, bone density, cardiovascular risk and quality of life?

### Is the Individual Truly GH Deficient?

GH secretion varies with age, and criteria for the diagnosis of GH deficiency differ in children compared with adults. Children secrete more GH than adults, in particular during the pubertal years, with GH levels peaking around mid to late puberty (earlier in girls than in boys), following which GH secretion gradually declines. In children, a peak GH response on two provocative tests of < 5 ng/ml suggests complete or severe GH deficiency, whereas a peak GH response between 5-10 ng/ml is termed partial GH deficiency. This is in contrast to adults, in whom a peak GH response of < 3 ng/ml with the insulin tolerance test, or <4-9 ng/ml on the GHRH-arginine test constitutes severe GH deficiency. The cut-off for diagnosis of GH deficiency in latepuberty and in young adults is, however, unclear. Given that GH has important effects on bone and body composition at this time of life despite growth being almost complete, and because GH levels, although declining, are still higher than in adults, it is suggested that a cut-off of 5ng/ml rather than 3ng/ml be used to define severe GH deficiency in this transition period.

Re-testing an individual previously diagnosed with GH deficiency is particularly important given the diagnostic inaccuracies associated with GH stimulation testing. In addition to the obvious false positives associated with the cut-offs used in childhood, fallacies may occur depending on the specific stimulation test selected, and the different GH assays in use. The insulin tolerance test, which is the gold standard for diagnosis of GH deficiency, is rarely used in children because of the risks from hypoglycemia, and the GHRH-arginine test, which is as accurate as the insulin tolerance test in adults without hypothalamic dysfunction, has not proven similarly useful in children. This has resulted in the use of a variety of provocative tests depending on the age of the child, side effects, and the preferences of the pediatric endocrinologist. In addition to diagnostic errors associated with the provocative stimulus used, there are errors observed related to lack of sex steroid priming prior to testing in children who are prepubertal or in very early puberty, particularly in situations of constitutional delay in growth and development.



In general, teenagers most likely to continue to test severely GH deficient are those with:

- (i) Multiple pituitary hormone deficiencies
- (ii) Peak GH response of < 5 ng/ml on initial testing
- (iii) Structural hypothalamic-pituitary and central nervous system abnormalities
- (iv) History of hypothalamic-pituitary irradiation.

Conversely, a normal peak GH response on repeat testing is more likely in individuals with:

- (i) Isolated idiopathic GH deficiency (30-70% subsequently have a normal response)
- (ii) Partial GH deficiency (~77% are normal on retesting) See Figure 1.

Overall, the peak GH response is normal in 20-87% of young adults who were diagnosed with and treated for GH deficiency in childhood. Some endocrinologists stop treatment in children with partial GH deficiency when the 10th percentile for height is achieved, or puberty begins; documentation of subsequent normal growth velocity in these children obviates retesting.

Currently, discontinuation of treatment and reassessment of GH secretory status is necessary before adult replacement can be initiated. Discontinuation of GH treatment for a period of three months is sufficient; reports exist of recovery of the GH axis even four weeks after interruption of GH therapy. It is interesting to note that at least one study has demonstrated normalized GH responses to stimulation testing in 29% of children even during daily GH replacement.

The European Society of Pediatric Endocrinology has recently proposed new guidelines based on serum IGF-I levels and GH stimulation testing (insulin tolerance test, arginine or glucagon). Continuation of GH therapy without interruption is suggested for teenagers with severe congenital or acquired hypopituitarism and multiple hormonal deficiencies. In adolescents with high likelihood of severe GH deficiency, measuring IGF-I after a month of discontinuing GH, and restarting GH treatment if serum IGF-I is  $< -2$  S.D.s is recommended. For adolescents with IGF-I levels  $> -2$  S.D.s, a GH stimulation test is suggested, with GH treatment to be restarted in patients with a low peak GH response. For adolescents with low likelihood of severe GH deficiency, both serum IGF-I and GH stimulation testing are recommended, with GH therapy to be restarted if IGF-I and peak GH response are low, to be stopped if both are normal, and further follow up suggested if results are discordant.

**"The recognition of a GH deficiency syndrome in adults necessitates identification of adolescents and young adults who may warrant continuation of treatment after statural growth is complete."**

### **What is the Ideal Dose of rhGH During the Transition from Adolescent to Adult GH Replacement?**

This is an important question, which has not yet been fully addressed. Based on higher GH concentrations in children and adolescents compared with adults, the replacement dose in children is higher (30-40 mcg/kg/day or 0.22-0.30 mg/kg/week) compared with adults (2-12 mcg/kg/day). The optimal dose during the transition from adolescent to adult replacement is likely somewhere in between, given that GH concentrations gradually decrease after puberty to adult levels. At least one study has suggested that a higher dose (25 mcg/kg/day) may have greater beneficial effects compared with a smaller dose (12.5 mcg/kg/day), although not all studies demonstrate a dose effect. Dose titration based on IGF-I levels for age is an alternative method of determining the optimum GH dose. This is even more important given the recently demonstrated differences in IGF-I levels depending on gender, with lower levels of IGF-I in women than in men.

### **Is a Drug 'Holiday' Possible and How Long Should This Last?**

Benefits of a drug holiday include temporary freedom from daily injections, and for the young adult to feel that plans made in childhood are being honored. Their sense of autonomy is maintained, and this period off GH allows for re-testing to be performed. For individuals that are not GH deficient on re-testing, there is no indication for restarting therapy. However, in individuals continuing to be severely GH deficient, the question arises as to when replacement should be resumed.

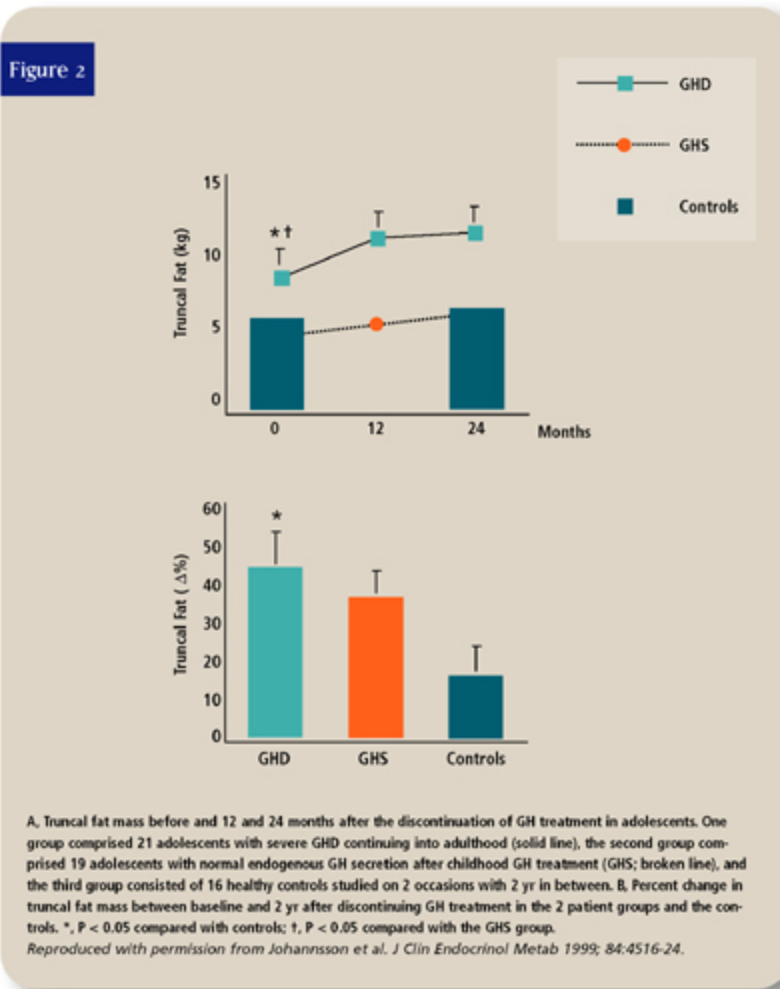
In addition to results of stimulation testing, this may be influenced by whether symptoms of GH deficiency develop in the young adult. Early development of clinical features makes the decision to restart therapy relatively simple. Features of adult GH deficiency include an increase in fat mass, a decrease in muscle mass resulting in decreased strength and exercise capacity, as well as a deterioration of quality of life.

However, an insidious development of symptoms may cause the individual to miss early features of adult GH deficiency, and this may be exaggerated by a subconscious reluctance to return to daily injections. In addition, some of the deleterious effects of GHD in adults, such as osteoporosis and increased cardiovascular risk are silent until fractures or cardiovascular events occur. Another major issue is that patients this age are often lost to follow up. They may no longer feel comfortable in a pediatrician's office, yet not have an established relationship with an adult care provider familiar with the use of GH. Individuals with multiple pituitary hormone deficits, those with evidence of severe GH deficiency, associated structural central nervous system abnormalities, and past history of irradiation are more likely than others to manifest the adult GH deficiency syndrome and be seen by an adult endocrinologist.

Of importance is the effect of GH on bone and body composition in the young adult. Healthy adolescents 17-21 years old exhibit increased lean body mass and handgrip strength over a two-year period but this does not occur in untreated GH deficient adolescents. Small studies in adolescents treated with GH during adulthood have demonstrated that fat mass increases by about 5% and muscle mass decreases commensurately within a year following discontinuation of GH, and reductions occur in muscle strength, muscle size and fiber area. Increases in trunk fat have been reported in GH deficient adolescents following discontinuation of GH therapy (Figure 2).

Adolescence and young adulthood are the periods of life when bone mass accrual is maximal, culminating in achievement of peak bone mass. This raises concern that cessation of GH replacement

Figure 2

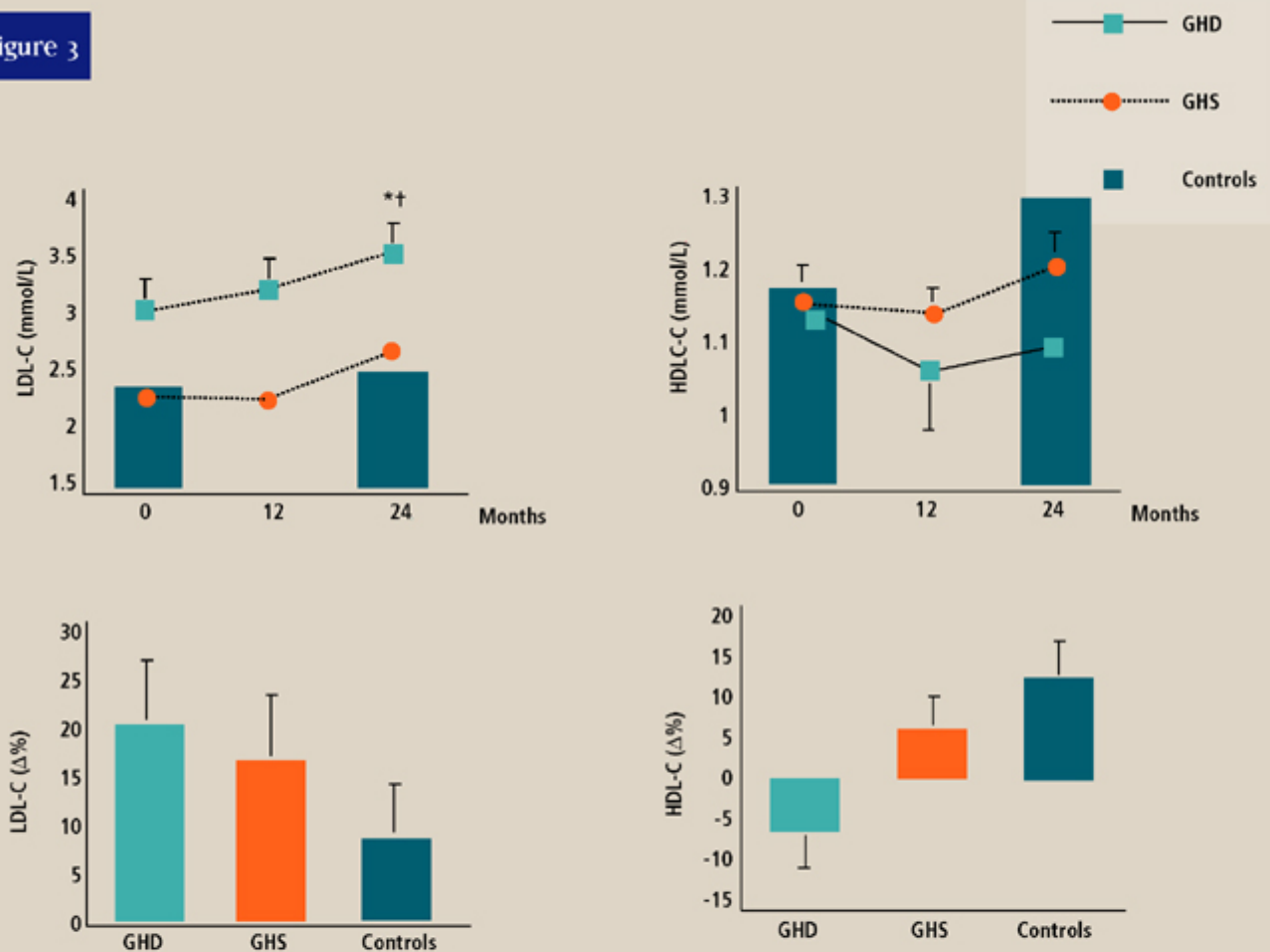


**"Discontinuation of therapy for a period of one to three months is advisable prior to retesting."**

may result in permanent deficits, particularly of bone mass, resulting in increased fracture risk in later life. A recent study of 40 GH deficient adolescents found no beneficial effects of GH replacement at a dose of 20mcg/kg/day, (i.e. about half the pediatric GH replacement dose), versus placebo on bone density, body composition, cardiac function, muscle strength, carbohydrate or lipid metabolism, or quality of life over a two year period. A trend towards lower bone density at the lumbar spine was, however, noted in the group receiving placebo. A significant difference may have been evident with a larger study, with a higher retention rate (only two thirds of the subjects completed the study) or with higher doses. Although continued increase in bone mass has been demonstrated up to two years after discontinuation of GH therapy, investigators have reported that attainment of peak bone mass is slower and ultimate peak bone mass lower than in controls, with rapid decline in bone density occurring two years after attainment of peak bone mass.

Beneficial effects on metabolic profiles and specific quality of life measures have been reported in other studies in GH deficient adolescents continued on GH after completion of growth (Figure 3). Larger studies are awaited to provide definitive information regarding the safety and duration of a drug holiday in older teenagers and young adults.

Figure 3



Upper panels: Serum LDL-C (left) and HDL-C (right) concentrations before and 12 and 24 months after the discontinuation of GH treatment in adolescents. One group comprised 21 adolescents with severe GHD continuing into adulthood (solid line), the second group comprised 19 adolescents with their own GH secretion (GHS; broken line), and the third group consisted of 16 healthy controls studied on two occasions with 2 yr in between. Lower panels: Percent change in serum LDL-C (left) and HDL-C (right) concentrations between baseline and 2 yr after discontinuing GH treatment in the 2 patient groups and the controls. \*,  $P < 0.05$  compared with controls; †,  $P < 0.05$  compared with the GHS group.

Reproduced with permission from Johannsson et al. *J Clin Endocrinol Metab* 1999; 84:4516-24.

## Conclusion

The recognition of a GH deficiency syndrome in adults necessitates identification of adolescents and young adults who may warrant continuation of treatment after statural growth is complete. Discontinuation of therapy for a period of one to three months is advisable prior to re-testing. A peak GH response of  $< 5$  ng/ml suggests the need for adult GH replacement therapy in transitional doses to begin with, to be gradually weaned to adult doses over time. Rapid resumption of GH replacement is especially recommended in individuals with clinical evidence of adult GH deficiency. However, complete reliance on symptoms alone may delay restarting therapy because there are no early symptoms of some features of GHD, or the onset of symptoms may be insidious, and because of the risk of loss to follow up. A drug

holiday is possible, but the duration of this period off GH should be balanced against risks of impaired bone mass accrual, increases in fat mass and decreases in muscle mass leading to poor muscle strength, increased cardiovascular risk and impaired lipid profiles, and a deterioration in quality of life. Current data suggest that the duration of discontinuation of GH therapy should not last longer than two years pending further data. Interaction between the pediatric and adult endocrinologists during the transition period is crucial to determine an optimal management plan for each young adult.

## References

1. Allen DB. Pediatrics. 1999; 104(4 Pt 2): 1004-10.
2. Attanasio AF, et al. J Clin Endocrinol Metab. 2005; 90:4525-9.
3. Clayton PE, et al. Eur J Endocrinol. 2005; 152: 165:165-70.
4. Mauras N, et al. J Clin Endocrinol Metab. 2005; 90:3946-50
5. Saggese G, et al. J Endocrinol Invest. 2004; 7:596-602.
6. Shalet S. Horm Res 2004; 62 (suppl 4):15-22.

---

## MASSACHUSETTS GENERAL HOSPITAL Acromegaly Patient Education Day

Dr. Karen K. Miller describes  
clinical approaches to  
acromegaly.



Dr. Beverly M.K. Biller explains the anatomy  
and physiology of the pituitary gland.

Nurses Karen Liebert and Karen Szczesiul  
answer patient questions about  
medical treatment of acromegaly.

On April 25, 2005, the Massachusetts General Hospital Neuroendocrine Clinical Center hosted patients and their guests for an informative Acromegaly Patient Education Day.



Attendees from 15 states learned about many aspects of the disorder from endocrinologists, nurses and an expert pituitary surgeon.

Slide presentations and a video of an actual transsphenoidal pituitary operation were highlighted by question and answer periods.

Patients with acromegaly shared their stories, providing a unique opportunity for patients with this rare disorder to meet other people with the same condition.



Neuroendocrine Unit Chief, Dr. Anne Klibanski, describes the clinical features of acromegaly and how the condition is diagnosed.

Neurosurgeon Dr. Brooke Swearingen explains transsphenoidal surgery to the attendees.



*“Excellent  
overview – easy  
to understand”*

*“Absolutely  
outstanding  
–  
great  
explanation  
of  
medications  
and side  
effects”*

*“I never knew  
a surgeon  
could  
have a sense  
of humor.”*

*“Invaluable to  
meet other  
patients with  
acromegaly”*