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Brain Injury and Pituitary Dysfunction

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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 hemmorage (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

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

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.

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 somahere totrophs, 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 monthsafter 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.

Table I. Hypopituitarism After Brain Injury: Summary of Recent Reports

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 thesetting 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 pituitarydeficiencies is appropriate in all patientswith a history of TBI or SAH within thefirst 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.

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Physiologic Cortisol Dynamics and Cushing's Syndrome in Pregnancy

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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.

Cushing's Syndrome During Pregnancy

Administration.

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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.

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 equivocalresults, 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 (withoutgadolinium contrast) is indicated, avoidingthe radiation associated with CT scanning.Alternatively, if the ACTH is normal orelevated, a pituitary MRI should be considered.Risks ofMRI in pregnancy have notbeen fully addressed and therefore the risks of this test must be weighedagainst thepotential benefits of diagnosis. Normal orequivocal findings on the pituitary MRIraisethe suspicion for an ectopic ACTHsource, although corticotroph adenomascan be too small tovisualize on head MRI.In these cases, inferior petrosal sinus samplingprocedures, with CRHstimulation, atspecialized centers have been performed inpregnant women to confirm the locationofACTH excess. In rare cases of pregnancyinducedCushing's syndrome, a source maynot bedetectable with imaging modalities.

Treatment

Due to the significant risks of hypercortisolemiafor themother and the fetus, anexpedient plan for cortisol normalization isnecessary. In most cases, thisentails surgicalresection of the hormonally activetumor. Close communication betweenendocrinologist, surgeon, anesthesiologistand obstetrician is important. Transsphenoidalsurgeryis the most commonapproach for resection of a pituitary tumorandadrenalectomy via laparoscopic oropen resection can be performed duringpregnancy. In casesof adrenal hyperplasia,pregnancy-induced Cushing's syndrome, orto decrease cortisol levels priorto surgicaltumor resection, medical therapy may beimplemented using adrenal steroidogenesisinhibitors, which are effective in decreasinghypercortisolemia. Although ketoconazoleisthe first line therapy in the non-pregnantpatient, this medication is contraindicatedinpregnancy 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 ofhypercortisolemiawith surgery, the patientis often adrenally insufficient, due to precedingsuppression ofthe HPA axis byexcess glucocorticoids. Therefore, replacementglucocorticoids are necessary; and inthe rare case of bilateral adrenalectomy,mineralocorticoid therapy is also indicated.Hydrocortisone orprednisone are acceptable choices for replacement because thefetus is protected from excessglucocorticoidlevels by placental 11-ß-HSD-2metabolism of these drugs. However,dexamethasoneshould be avoided in pregnancybecause it is not metabolized by 11-ß-HSD-2 and thus crosses the placenta. Thestandard replacement dose required duringpregnancy 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 laboratorytests 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.

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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 identifytruly GHdeficient individuals rather than continue GH

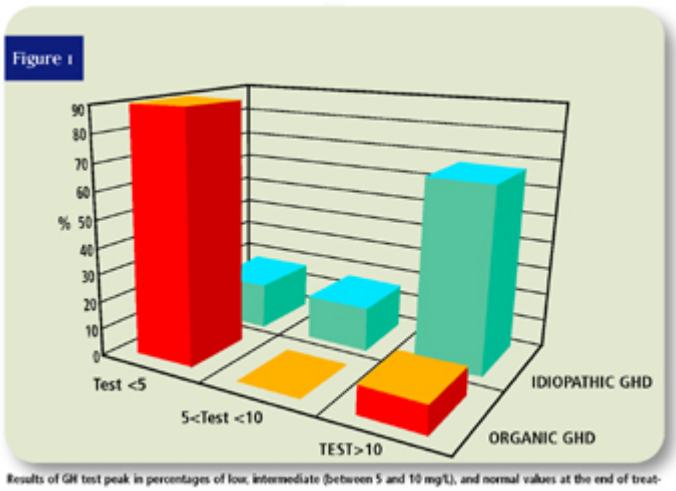
replacement in all young adults, some of whom may no longer test as GH deficient. This is particularly important because GH therapy is not without certain side effects; amongst these the risk of developing impaired glucose tolerance and less commonly, frank diabetes. The other important aspect is the 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 partialGH 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 importanteffects on bone andbody composition at this time of life despite growth beingalmost complete, and because GH levels,although declining, are still higher than inadults, it is suggested that a cut-off of 5ng/ml rather than 3ng/ml be used todefine severe GH deficiency in thistransition period.

Re-testing an individual previouslydiagnosed with GH deficiency is particularlyimportant given the diagnostic inaccuraciesassociated with GH stimulation testing.In addition to the obvious false positivesassociatedwith the cut-offs used inchildhood, fallacies may occur dependingon the specificstimulation test selected,and the different GH assays in use. Theinsulin tolerance test, which is thegoldstandard for diagnosis of GH deficiency, israrely used in children because of the risksfromhypoglycemia, and the GHRH-arginine test, which is as accurate as theinsulin tolerance test inadults withouthypothalamic dysfunction, has not provensimilarly useful in children. This has resultedinthe use of a variety of provocativetests depending on the age of the child,side effects, and thepreferences of the pediatric endocrinologist. In addition todiagnostic errors associated with theprovocative stimulus used, there are errorsobserved related to lack of sex steroid primingprior totesting in children who are prepubertalor in very early puberty, particularlin situations of constitutional delay in growth and development.



Results of GH test peak in percentages of low, intermediate (between 5 and 10 mg/L), and normal values at the end of treat-

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-pituitaryand central nervous system abnormalities(iv)Historyof hypothalamic-pituitaryirradiation.

Conversely, a normal peak GH responseonrepeat testing is more likely in individualswith:

(i) Isolated idiopathic GH deficiency(30-70%subsequently have a normalresponse)
(ii) Partial GH deficiency (~77% arenormal on retesting) SeeFigure 1.

Overall, the peak GH response is normalin 20-87% of young adults who werediagnosed with and treated for GH deficiencyin childhood. Some endocrinologistsstop treatment inchildren with partialGH deficiency when the 10th percentilefor height is achieved, or puberty begins;documentation of subsequent normalgrowth velocity in these children obviates retesting.

Currently,discontinuation of treatmentand reassessment of GH secretory status isnecessary before adult replacement can beinitiated. Discontinuation of GH treatmentfor a period ofthree months is sufficient; reports exist of recovery of the GH axiseven 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 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."

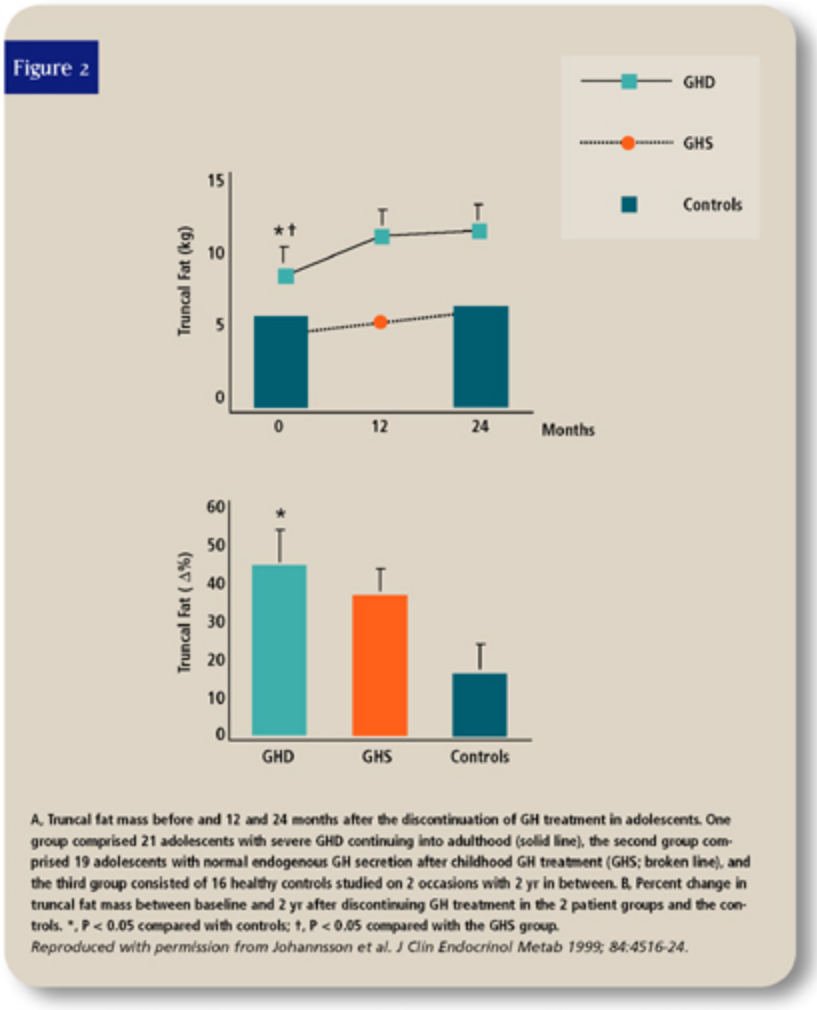
The European Society of PediatricEndocrinology has recently proposed newguidelines based on serum IGF-I levels and GHstimulation testing (insulin tolerancetest, arginine or glucagon). Continuationof GH therapy without interruption is suggested for teenagers with severe congenital or acquired hypopituitarism 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, withGH treatment to be restarted inpatients with a low peak GH response. Foradolescents with low likelihood of severeGH 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 suggestedif results are discordant.

What is the Ideal Dose of rhGH DuringtheTransition from Adolescent to Adult GHReplacement?

This is an important question, which hasnot yet been fully addressed. Based onhigher GH concentrations in children andadolescentscompared 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 transitionfrom 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.



A, Truncal fat mass 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 normal endogenous GH secretion after childhood GH treatment (GHS; broken line), and the third group consisted of 16 healthy controls studied on 2 occasions with 2 yr in between. B, Percent change in truncal fat mass 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.

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 re-start 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.

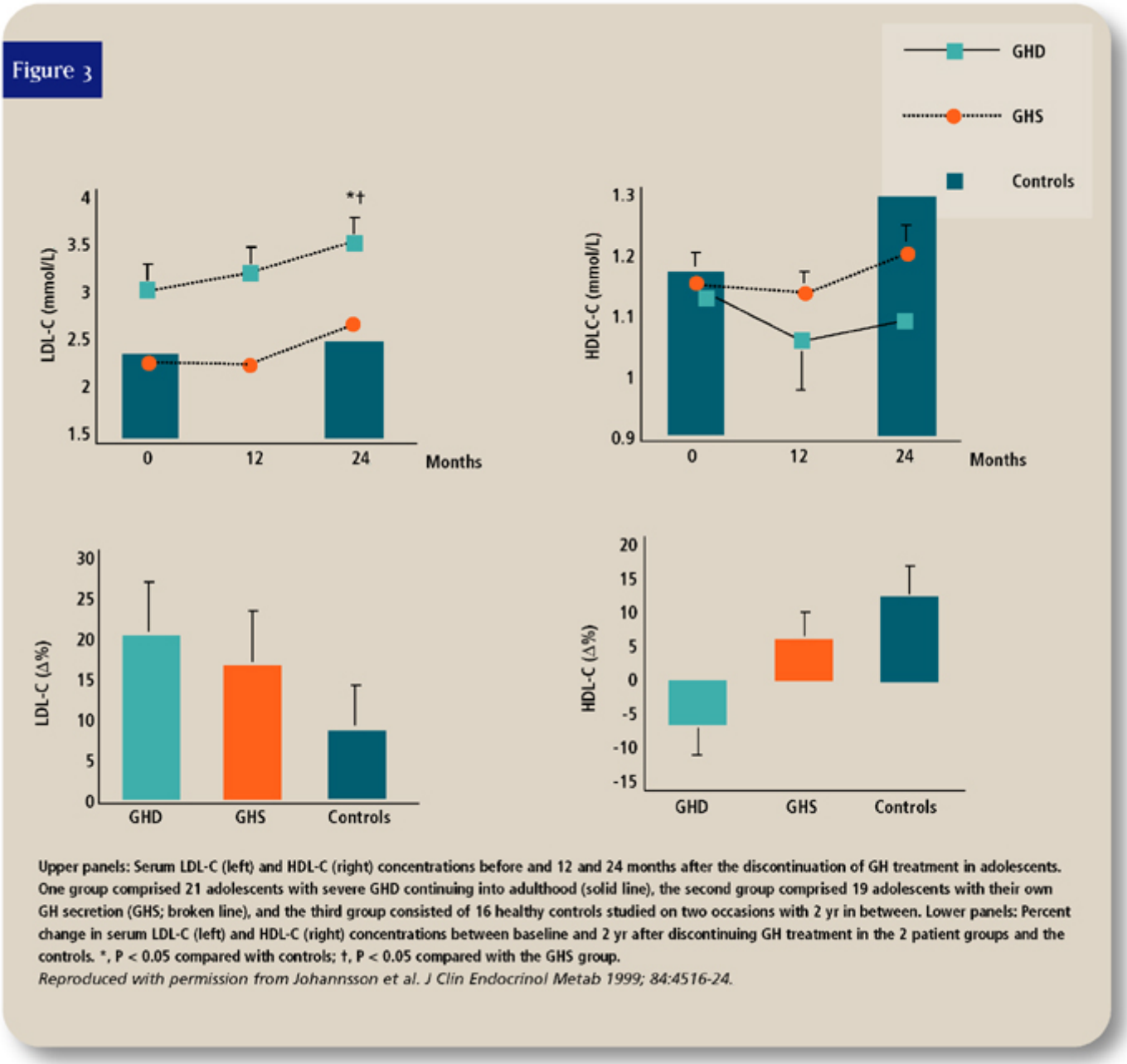
"Discontinuation of therapy for a period of one to three months is advisable prior to retesting."

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

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 GHreplacement 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.



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.

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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.

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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"