ISSUES IN THE TRANSITION FROM CHILDHOOD TO ADULT GROWTH HORMONE THERAPY

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ABSTRACT. The consequences of severe growth hormone deficiency (GHD) in adults and the beneficial effects of GH replacement therapy are clear. However, the majority of children who have a diagnosis of GHD and who are treated with GH do not have permanent GHD and will not require treatment during adulthood. Several issues must be considered in selecting candidates for adult GH treatment and transitioning their care from pediatrics to adult medicine. Counseling about possible lifelong treatment should focus on children with panhypopituitarism and those with severe isolated GHD that is associated with central nervous system abnormalities. When to terminate growth-promoting GH therapy should be guided by balancing the high cost of late-adolescent treatment with the attainment of reasonable statural goals. Retesting for GH secretion is appropriate for all candidates for adult GH therapy; the GH axis can be tested within weeks after the cessation of treatment, but confirming an emerging adult GH state with body composition, blood lipid, and quality-of-life assessments may require 1 year or more of observation. Selecting patients for lifelong adult GH replacement therapy will present diagnostic, therapeutic, and ethical problems similar to those in treating childhood GHD. The experience and expertise of pediatric endocrinologists in diagnosing and treating GHD should be offered and used in identifying and transitioning appropriate patients to adult GH therapy. Pediatrics 1999;104:1004–1009;

clonidine test, growth hormone deficiency, hypothalamic-pituitary region, insulin tolerance tests, multiple pituitary hormone deficiency.

ABBREVIATIONS. GHD, growth hormone deficiency; GH, growth hormone; IGHD, isolated GHD; MPHD, multiple pituitary hormone deficiencies; ITT, insulin tolerance test.

It is becoming increasingly clear that adults with growth hormone deficiency (GHD) have physiologic (eg, greater subcutaneous and visceral fat mass, subnormal muscle mass, lower bone mineral density, lower cardiac function, higher low-density lipoprotein cholesterol level) and functional (less physical performance, cognitive function, and sense of well-being) impairments that are at least partially reversed by GH replacement therapy. The prospect of lifelong treatment with GH for certain children with GHD is a significant departure from traditional GH therapy, which was confined to childhood and was dictated by statural goals. It also presents several new challenges in preparing, identifying, and transitioning appropriate patients from childhood to adult GH therapy.

In this article, I discuss five important issues in the transition from childhood to adult GH therapy: 1) Which children should and should not be counseled to expect adult treatment? 2) When is it appropriate to switch from higher-dose, higher-cost growth-promoting treatment to lower-dose adult treatment? 3) Should GH treatment be interrupted between childhood and adulthood and, if so, for how long? 4) How should the need for GH replacement therapy be assessed in young adult candidates? 5) What degree of advocacy is appropriate in counseling competent young adults with GHD who are reluctant to continue treatment?

PREPARING GH-TREATED CHILDREN

The value of GH treatment in children with severe GHD is now well established. If treated early and consistently, children affected reach an adult height within the normal range.1 The current clinical practice is to discontinue GH therapy when their linear growth is either complete or their height is in the normal range for adults, and most children who are treated with subcutaneous GH look forward to eventual freedom from daily injections. Because it is likely that some of these patients would benefit from treatment during adulthood, it is important to provide guidance about continued treatment.

Which children should be prepared for adult GH treatment? The answer is complicated by the fact that...
most children who are treated with GH do not have permanent or complete GHD, but rather have insufficient secretion of GH to support normal childhood growth. When children with isolated GHD (IGHD) are retested after GH replacement therapy has been interrupted, between 30% and 70% will have a normal GH response. Children with a previous diagnosis of partial GHD (ie, peak stimulated GH levels of 5 to 10 μg/L or low 24-hour integrated GH secretion) are particularly likely to have normal results on posttreatment testing (Fig 1). The results of provocative testing of GH secretion are normal in 20% to 87% of young adults who had a diagnosis of GHD and were treated for it during childhood. Patients with IGHD are more likely to have normal GH responses on retesting than are patients with multiple pituitary hormone deficiencies (MPHD). In general, the greater the degree of MPHD, the lower the GH response to insulin-induced hypoglycemia (Fig 2). At a threshold GH level of 4.5 μg/L, disparate results between two provocative tests are much more likely in patients with IGHD. When data from several studies are considered together, ~60% of the children with a former diagnosis of GHD would not be eligible for continued GH treatment in adulthood if the criterion of a GH level of 5 μg/L were applied. Clearly, a former diagnosis of GHD in childhood, particularly IGHD, is insufficient to conclude that a person will have GHD for life.

Several explanations for this apparent normalization of GH secretion in such a large proportion of patients are possible. Traditionally, the diagnostic threshold for GHD has been defined arbitrarily, and the reproducibility of a GH response to provocative testing within an individual is not high. For this reason alone, it is not surprising that some of those who were at one time considered to have GHD may not meet the diagnostic criteria for GHD at another. Second, it is likely that the hypothalamic control of GH secretion matures, most likely as a result of the greater levels of sex steroids during puberty. Children with constitutional delay in growth and puberty are known to have periods of low GH secretion, particularly during the years immediately before puberty. In this setting, accurate assessment of GH secretory capability requires sex-steroid priming.

If this is not taken into account, this normal variant growth pattern can be misdiagnosed as GHD and also result in subsequent observations of “restored GH secretion” in these GH-treated children. Short-statured school children with responses to GH provocative testing just below the traditional diagnostic cutoff of 10 μg/L, often described as “partially” GH-deficient, also appear likely to have increased secretion of GH in response to pubertal development. Finally, it remains possible that transient GHD in childhood actually occurs, but longitudinal studies that support this are lacking.

On the other hand, the incidence of severe GHD appears to increase in persons who underwent radiation treatment to the hypothalamic–pituitary region during childhood. Adults who have been treated with hypothalamic–pituitary irradiation at a dose of 37.5 to 45 Gy have increasing severity of GHD with time. In one study, the proportion of patients with radiation-induced childhood-onset GHD who had a peak GH level <4.5 μg/L on the insulin tolerance test (ITT) increased from 49% to 56% on retesting. Based on these data, it appears reasonable for pediatric endocrinologists to prepare children and their families for probable GH treatment when severe GHD is part of MPHD or is associated with defined structural central nervous system abnormalities. Patients with a diagnosis of variable degrees of GHD after hypothalamic–pituitary irradiation can be advised that because the severity of this deficiency may increase, the need for GH replacement therapy during adulthood should be reassessed. Finally, current information suggests that patients with IGHD without structural causes, and particularly those with...
borderline results on diagnostic tests of GH secretion, can be advised that they are not likely to require adult GH treatment.

**DISCONTINUING GROWTH-PROMOTING GH THERAPY**

Deciding to discontinue GH therapy can be difficult, and requires that additional height potential, cost, discomfort, and inconvenience be considered. The continued relevance of distinguishing between GH treatment to overcome disabling short stature and GH augmentation of normal stature is sustained primarily by the high cost of GH. A cost–benefit analysis of the height gained as a result of GH treatment shows a steep rise in the number of dollars spent per centimeter of height gained in the later stages of adolescence (Fig 3). In particular, the last year or two of treatment aimed at achieving the genetic potential for growth of the (now heavier) adolescent can be particularly costly. Consequently, determining an appropriate endpoint for traditional-dose, growth-promoting GH therapy remains problematic.

In consideration of recent documentation of normal GH secretion in the majority of children with a previous diagnosis of IGHD, discontinuing GH treatment after the onset of puberty but before the attainment of near-final height appears reasonable in many of these children. It has been our practice in those with a diagnosis based on provocative GH test results between 5 and 10 μg/L to attempt a trial of discontinuing GH when a height at the 10th percentile is reached or evidence of puberty is noted. The subsequent documentation of normal growth in many of these children obviates retesting to determine whether they are candidates for adult GH treatment. Furthermore, there are no data indicating that patients with partial GHD (ie, a GH response of 5 to 10 μg/L) are at risk for the development of the adult GHD syndrome.

Even in patients with a diagnosis of IGHD based on a peak GH value of <5 μg/L, it appears that a significant proportion of those without identifiable midline or central nervous system defects will be GH-sufficient after puberty and that costly GH treatment to final height may be unnecessary.

Given this uncertainty, to what extent should it be expected that private or government medical insurance would support the treatment of short stature? For otherwise normal children with IGHD, most of whom will not have permanent, severe GHD, it could be argued that treatment should be continued until a height that is not considered a disability (ie, just within the normal adult range) is achieved. Because therapy beyond that point makes the recipients taller than other normal-statured adults, continued GH treatment for short stature then becomes augmentation of normal stature. Families could seek continued therapy, and physicians could choose to treat such children (but they are justified in not feeling an obligation to do so); however, it should not be expected that public funds should be used to pay for such therapy.

On the other hand, for the relatively small proportion of adolescent patients with severe, unequivocal GHD that is associated with either MPHD or structural central nervous system lesions, the data cited above suggest that GH is important for acquiring normal body composition and bone mineral density. Cross-sectional data on patients with severe childhood-onset GHD after several years without GH treatment show marked physiologic abnormalities. Given the low mean final heights of the patients in these studies (−2 standard deviations), however, it remains unknown whether these findings indicate the effects of GH withdrawal at final height or suboptimal GH treatment during childhood and adolescence. Until better data become available on the dose of GH that is necessary to optimize GH-mediated metabolic effects in severely GH-deficient adolescents, continued traditional-dose treatment of these patients to near-final height appears prudent.

**INTERRUPTING GH TREATMENT**

Discontinuing GH treatment and reassessing the GH secretory axis is currently required before adult GH therapy can be initiated. The decision about when to stop GH treatment remains subjective and individualized, but data are available on the interval necessary after the discontinuation of GH before retesting produces valid results. In one study, 7 of 8 children with a diagnosis of IGHD had normal results on GH secretion studies 3 months after having completed GH therapy. Cacciari et al retested a group of children with IGHD 4 weeks after their GH replacement therapy had been interrupted and found that 20.6% of them had normal GH peak responses to two provocative tests. In a subsequent, more extensive study, the same investigators retested 152 children during daily GH replacement therapy and found that 29% of them had normalized GH responses. In summary, an intact GH axis is recovered promptly after exposure to exogenous GH, and retesting can be performed with confidence at 3 months, and perhaps as early as 4 weeks, after the cessation of treatment.

A strategy aimed at preventing GHD-related morbidity in adulthood might discourage interrupting GH treatment in patients in whom permanent complete GHD is almost certain (eg, after craniopharyn-
gioma). The data on retesting cited above suggest that a very brief interruption of therapy may be sufficient to make informative provocative testing possible. There may be value in preventing the insidious onset of the adult GHD syndrome, which is frequently unrecognized by patients who are understandably reluctant to return to daily subcutaneous injections. Reducing the dose of GH rather than discontinuing it entirely could also minimize the occurrence of the adverse effects that are associated with the reinstitution of therapy. However, the necessity and efficacy of uninterrupted GH therapy in preventing the development of the adult GHD syndrome remain to be shown in placebo-controlled trials. In the current absence of reliable predictors of the consequences of discontinuing GH therapy, it appears that a period of observation without GH is appropriate in all potential candidates for adult GH treatment.

Is There an Optimal-length GH-treatment “Holiday”?  
A short break from daily injections may be insufficient to alleviate the “GH burnout” that adolescents who have been treated for many years often experience. Patients who had looked forward to eventual freedom from injections may feel that previous promises have been broken and may resent their loss of autonomy in making decisions about their health care. If GH treatment is restarted before manifestations of the adult GHD syndrome are recognizable, their skepticism about the value of the treatment also might be reinforced. On the other hand, there are risks associated with a prolonged period of no treatment, including breaking the routine of administering GH, losing patients to follow-up, and patients’ adapting to (and accepting) the adult GHD state. Each of these factors could undermine the success of long-term adult GH replacement therapy.

One approach to deciding on an appropriate length of time without GH treatment is suggested by differentiating eligibility, a designation based on GH testing, from the clinical indication for GH treatment. In patients at high risk for adult GHD (ie, those with MPHD and other complete GHD), confirming persistent severe GH can, and probably should, be done within weeks to months after the GH treatment has been stopped. Patients with a response to provocative GH retesting of <5 μg/L are most likely to be affected by the adult GHD syndrome and could be considered eligible for treatment. However, this arbitrary threshold undoubtedly will falsely include (and may falsely exclude) many patients in whom the adult GHD syndrome will develop, and the prognosis for adult patients with a provocative GH response of 5 to 10 μg/L is not known. The low specificity of a single-test threshold for diagnosing childhood GHD leads most pediatric endocrinologists to await clinical confirmation of a so-called GHD syndrome (poor growth, delayed skeletal maturation, lack of other explanations for growth failure, and other confirmatory laboratory test results) before instituting treatment. Similarly, after patients at high risk for adult GHD have been identified, it seems reasonable to base subsequent decisions about the clinical indications for adult GH treatment not on provocative testing alone, but also on the physiologic changes that are observed in them after the discontinuation of GH treatment for childhood GHD.

This concept is supported by the recent recommendation “that all patients with a reduced GH response [ie, <5 μg/L] be monitored for a period of at least 5 years, with special emphasis on body composition, serum lipid levels, and physical performance.” However, few studies have examined the rate at which deleterious effects occur after the discontinuation of GH treatment. One study in 8 patients with peak GH responses of <5 μg/L found that the proportion of body fat (measured by skinfold thickness) increased from 19.5% ± 8.6% to 24.1% ± 9.5% during 1 year without GH treatment. Muscle mass and muscle strength decreased by ~5% to 10% during the same period. A smaller study in 6 adolescent boys found an increase in the amount of body fat (measured by bioimpedance analysis, which may overestimate the changes in body fat in patients with GHD) of 4.1 ± 2.2 kg in the first 3 months after GH had been discontinued. Bone mineral density does not appear to be affected adversely in adults with GH whose GH treatment had been interrupted for at least 6 months. Longitudinal information on changes in cardiac function, lipid profiles, and quality-of-life measures after GH treatment is not available. Given the various degrees and causes of GHD, an observation period of 5 years may be long enough in some, but too long in others. It is likely that determining a patient’s risk factors for manifestations of adult GHD will be essential in choosing the appropriate frequency of body composition analyses and other assessments and the threshold for pharmacologic intervention.

ASSESSING THE NEED FOR ADULT GH TREATMENT

Determining eligibility for adult GH treatment begins with documenting abnormal GH secretion. Pharmacologic GH stimulation tests, the diagnostic limitations of which are well known, remain useful for this purpose; the diagnostic threshold level—currently <5 μg/L but certain to be debated—will identify virtually all patients with complete GHD as well as some with partial GHD, who may or may not require GH treatment. The ITT has high diagnostic accuracy in adults, and induces a more profound GH release than Arg, glucagon, clonidine, levodopa, or exercise (Fig 4). Pediatric endocrinologists have been reluctant to use the ITT (particularly when suspicion for severe GHD is high) for fear of adverse events, but the test appears safe in adults with GHD when it is performed in experienced endocrine units. A recent consensus conference named the ITT as the diagnostic test of choice for the diagnosis of adult GHD. Of particular relevance to the diagnosis of GHD in adults, an ITT with adequate hypoglycemia distinguishes GHD from the reduced secretion of GH that occurs with normal aging and with obesity. An alternative provocative test of GH secretion in patients with contraindications to the ITT is the combined administration of Arg and growth hor-
mone—releasing hormone. Arg or glucagon alone has less diagnostic validity, and clonidine does not appear to be as useful a provocative agent for GH secretion in adults.

Substantial differences in the provoked GH levels between two provocative tests are common in patients with IGHD, but are rare in patients with MPHD. Consequently, one provocative test result is currently deemed adequate in adult patients with identifiable hypothalamic–pituitary disease or concomitant MPHD. In patients with childhood-onset IGHD, a high proportion of whom may not have permanent GHD, two tests are recommended. The diagnostic value in adults with childhood-onset GHD of other biochemical markers of GH action, such as the serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3, appears comparable with that in children with GHD. A level of insulin-like growth factor I below the normal range for age is suggestive of GHD in adults, particularly in the presence of MPHD, but is affected by other conditions such as malnutrition, hepatic disease, poorly controlled diabetes mellitus, and hypothyroidism.

A documentation of low GH levels, however, may not equate with the need for adult GH therapy. The criteria for the clinical indication for GH therapy will vary depending on whether the goal is to prevent the adult GHD syndrome or to treat it. Because the evolution of the adult GHD syndrome after post-GH treatment diagnostic testing remains unclear, some clinicians strongly recommend thorough documentation of physiologic changes that indicate GHD before beginning treatment. Recently published consensus guidelines, on the other hand, state that the goal of GH replacement therapy in adults is to correct abnormalities associated with adult GHD, but do not state whether such abnormalities should be identified and assessed before treatment.

Ancillary studies of body composition, bone mineral density, lipid profiles, and quality-of-life measures clearly make determining the need for adult GH treatment more complex, but they also reduce overreliance on tests of GH secretion alone. In pediatrics, adhering to the concept that (arbitrary) diagnostic cutoffs could identify GHD eventually necessitated relaxing the diagnostic thresholds to permit access to GH for children with borderline GHD and, later, other GH-responsive children. This facilitated early intervention for childhood GHD and increased the final heights in GH-treated children, but also resulted in the treatment of many children in whom GHD is no longer present in adulthood. The statement that “it is simplistic and, ultimately, unrealistic to believe that a single biochemical assay can be relied on” to establish a diagnosis of GHD applies to adults as well as to children. If GH levels alone are used to define a clinical indication for adult GH therapy, interpreting borderline GH levels (eg, 4.9 or 5.1 µg/L), making adjustments for the various GH assays used, and resolving the differences between two provocative test results in a patient with IGHD will lead to diagnostic and therapeutic controversies similar to those that have been recurring themes in the treatment of childhood GHD.

**Fig 4.** Peak GH responses to a variety of provocative agents. The horizontal bars indicate the medians. Reproduced with permission (Rahim et al).17

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**THERAPEUTIC ADVOCACY AND RESTRAINT**

Despite accumulating evidence that GH replacement therapy has many salutary effects in adults with profound GHD, some patients at high risk for the adult GHD syndrome will likely decline therapy, citing the inconvenience of daily injections and promises that their therapy would stop once their growth was complete. On the other hand, some patients who are less likely to require or to benefit from GH therapy (eg, those with partial IGHD) may demand testing and, if their GH levels are low, treatment. Recognizing that the patient is now a competent young adult rather than the child with the original diagnosis of GHD, how much therapeutic advocacy or restraint on the part of the pediatric endocrinologist is warranted?

There is, of course, no clear answer to this question. Some guidelines, however, will be helpful in the transition. First, given the pediatric endocrinologist’s long-term relationship with and detailed knowledge of the patient, his or her commitment to work through this transition with the patient should be made clear. Agreeing on the duration of the drug holiday and making firm arrangements for follow-up appointments are good starting points. Second, the pediatric endocrinologist should define, and reorient if necessary, the locus of the decision-making to the patient and the physician—the patient’s parents should be taken out of the picture. Third, providing good advice begins with providing good facts: accurate and clear information on the adult GHD syndrome and its treatment is available, and can be given to the patient. The patient also can be referred to selected websites with which the physician is familiar. Fourth, if the patient is at high risk for the adult GHD syndrome, objective baseline data (body composition, lipid profiles, exercise testing results) should be gathered that may help support or refute the indication for GH therapy at a later date. Fifth, the patient should be assured that any future
prescribing of GH would be based on evidence of adverse effects attributable to GHD and would be on a trial basis with both objective and subjective measures, and whether to continue it would be decided accordingly. Sixth, the pediatric endocrinologist should establish working relationships with adult endocrinologists and other adult physicians who would also care for the patient during this early treatment period. Finally, the physician must be prepared to honor and respect the autonomy of a legally and ethically competent young adult patient, who, regardless of the physician’s viewpoint or best efforts, might have different ideas about the value of adult GH treatment.

Numerous studies now indicate that adults with GHD are both physically and psychologically less healthy than their age-matched peers and that GH replacement therapy results in substantial and sustained benefits. It is likely that in the future GH replacement therapy will be a routine component of hormone-replacement therapy in adults with hypopituitarism. Nevertheless, the treatment of adult GHD is now in its infancy, and much remains to be learned about selecting patients for what is likely to be lifelong therapy. For selected patients who had been treated previously with GH during childhood—namely, those with MPHD, those with severe IGHD associated with central nervous system abnormalities, and some who had undergone irradiation treatment—strong encouragement to proceed with evaluation for and treatment of adult GHD appears warranted. For those with partial GHD, the beneficial effects (if any) remain unknown. Consequently, for the much larger number of patients who have been treated for IGHD, considerable restraint in diagnosing and treating adult GHD based on provocative testing of GH secretion alone in the absence of confirmatory clinical indicators (eg, abnormal body composition or bone mineralization) also appears reasonable. Pediatric endocrinologists, who are well aware of the difficulties of diagnosing GHD and equitably and cost-effectively prescribing GH, can help determine which young adults still require GH treatment by taking an active role in their transition to adult care.

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REFERENCES

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