

Growth Hormone Therapy for a Child With Severe Cognitive Impairment

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The expansion of growth hormone therapy over the last 3 decades has allowed for treatment of short stature for more children, resulting in increased height for many. However, treatment of idiopathic short stature remains controversial. Treatment decisions for disabled children with idiopathic short stature are even more complicated. We discuss a specific case of short stature in a disabled child and grapple with the ethical issues involved in the use of growth hormone.

abstract

The development of recombinant growth hormone (GH) in 1985 expanded the use of GH from children with growth hormone deficiency (GHD) to nondeficient children with short stature, including idiopathic short stature (ISS) in 2003.¹ The expansion raised ethical questions regarding the acceptable use of GH. Those who are proponents of treatment argue that ISS is a pathologic diagnosis affecting quality of life and is treatable with a relatively safe medication to improve outcomes.² Those who are opponents of such treatment contend that short stature is a normal variant in which treatment to improve height creates risk and does not improve quality of life.³ A complication to this ethical dilemma is the treatment of children who are mentally disabled with unexplained short stature. Unique ethical issues must be considered regarding the use of GH to increase height in children who are mentally disabled with unexplained short stature.

THE CASE

A boy who is 14 years and 5 months old presents to the endocrine clinic for the evaluation of short stature. The evaluation reveals extreme short stature with height at -3 to -4 SD

scores. The patient had craniofacial anomalies (including a hypoplastic mandible, temporal bones, and ossicles), microtia, conductive hearing loss due to his bony anomalies, and developmental delay. He obtained bone-anchored hearing aids at age 6 years. His recent intellectual functioning was at a 5-year-old level. He participates in a fifth-grade classroom but receives significant educational support with some improvement in recent years. He has minimal capacity to live independently as an adult. He is physically capable and currently plays on a soccer team.

His growth records reveal consistent height velocity over several years along the -3 to -4 SD score curve. His bone age is delayed by 1.4 years, resulting in a predicted adult height of 61 in compared with the calculated midparental height of 68 in. Hormonal assessment reveals no evidence of GHD, thyroid disease, or other underlying causes of short stature. Previous genetic evaluation, including chromosomal microarray, did not yield a unifying diagnosis.

His family seeks treatment with GH to increase his height despite no identifiable cause of short stature. He is categorized as having ISS, although it is suspected he has an unknown

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genetic mutation resulting in his clinical phenotype. The US Food and Drug Administration has approved treatment with GH therapy, making treatment for this patient medically possible given the availability of GH and severity of his short stature, but it remains unclear if treatment should occur. During discussions of his possible height outcome and whether GH therapy is appropriate, the family asks, “What would you do?”

VINCENT HORNE, MD, COMMENTS

GH therapy might provide benefits for these children who are short. Additional inches may improve physical interactions in a work space, improve emotional adaptation, and enhance social inclusion, resulting in overall better quality of life.⁴ Some children who are disabled may also benefit from improved metabolic function, anaerobic muscle strength, and bone density after GH therapy.⁵ These effects may outweigh the burden of treatment for some children.

However, increased height in the child who is disabled may not be a benefit.⁶ If an individual who is disabled requires lifelong dependent care, short stature may make care easier. Some children who are disabled may not perceive a stigma from their short stature or may even benefit by being treated as younger than they are during childhood and adolescence.

Potential adverse effects of GH treatment include increased intracranial pressure, hip abnormalities during growth (including slipped capital femoral epiphysis), insulin resistance, and the theoretical risk of malignancy.⁷ Daily injections, blood draws for growth factor concentrations, and regular travel for clinic appointments are also burdens.

Mental disability makes autonomous decision-making more complex. In this case, the child did not have decisional capacity. Thus, the family and the doctors would have to make a decision based on their perceptions of what was in the patient’s best interest.

Caregivers must also contemplate the just use of a costly resource. GH therapy costs \$30 000 to \$50 000 per inch of growth.⁸ Insurance coverage varies. Many insurance companies require previous approval based on test results. It may also be unjust to use scarce resources for a child who is disabled who may not achieve a significant benefit to therapy. It would conversely be unjust to deny children who are disabled and short the option of GH therapy if there is a possibility of benefit when many nondisabled children are treated for ISS.⁹

Ultimately, caregivers and providers must weigh the risks of treatment, benefits of therapy, cost and resource allocation, justice for the child, and the child’s psychological and physical well-being. Researchers have not clearly proven that increased height changes quality of life outcomes for ISS.¹⁰ For children who are disabled and have ISS, outcomes are even less clear. Caregivers must weigh their own goals of therapy against the potential risks and benefits.

The family in the present case sought a paternalistic suggestion, asking, “What would you do?” I would recommend that, when asked that question, doctors should refrain from answering, and instead, guide the discussion back to the family’s preferences. Ultimately, given the uncertainties, it is their decision to make.

DAVID B. ALLEN, MD, COMMENTS

As exemplified by the vignette’s concluding question, access to GH for height therapy (ie, GH treatment

to increase the growth rate and height in a child without GHD) is strongly influenced by prescribers’ perspectives on the risks and benefits of growth promotion for a particular child.¹¹ One approach to formulating an ethical response to the parents’ question is to consider how the many issues surrounding GH treatment should be addressed in an informed assent discussion.¹²

For this child who has a cognitive disability and a predicted adult height of 5 ft 1 in, the parents are likely primarily concerned about the physical disability and secondarily concerned about the emotional and/or psychological consequences of extreme short stature. They want to help their child become closer in height to the statistical normal range. It is reasonable to think that this might make his life better. Such a goal is consistent with the proper role of medicine. Extreme short stature can be disabling. Treatment to overcome such a disability is medically desirable and appropriate.¹³ It is not an effort to merely lessen an “unlucky” competitive disadvantage by enhancing (already normal) height, performance, or appearance.¹⁴ For clinical situations in which GH could ameliorate disabling short stature, the underlying cause of growth impairment is not ethically relevant to entitlement. That is, such children all share the following central, equally valid concern: “I am short and need to be taller.”¹⁵

Although likely less central to this case, GH for height treatment is commonly sought to alleviate perceived psychological distress attributed to shortness. However, although less favorable characteristics are often attributed to short people, psychosocial problems are not more common among youths who are short in stature. Presumptions that short stature is predictably and causally related to negative outcomes

exemplify a “focusing illusion” in which judgments about a characteristic derived from a subset are applied globally to all subjects with the characteristic.¹⁶ On the other hand, and relevant to the child in this vignette, discounting possible psycho-social disability and disappointment due to shortness a priori in children with cognitive disabilities (eg, Prader-Willi syndrome) may be inaccurate, unfair, and should be resisted as a disqualification from access to treatment.

However, a pediatric care provider’s duty to a child involves not only providing necessary treatment but also protecting him or her from unnecessary or ineffective interventions. Although parental intentions in this case are reasonable, what can they be honestly told about GH effectiveness? GH therapy for children who are short and not GH deficient increases mean adult height by ~1.0 cm per year of treatment.¹⁷ Importantly, however, response is variable and influenced positively by younger age at baseline, delay in skeletal maturation, and taller parents, none of which are present in this case. Accordingly, an assent discussion should make clear that this child is likely to be a “less than average” responder. Given that he has a bone age of 12 to 13 years and will therefore be eligible for ~4 years of treatment before epiphyseal fusion, his adult height might be increased by 3 to 5 cm (ie, 1.5 in; from 61 to 62.5 in based on reported prediction). In this pubertal-aged child, doubling the dose of GH during puberty¹⁸ or coupling GH treatment with aromatase inhibition¹⁹ until epiphyseal closure might increase adult height slightly more. Parents should also know that, even if GH-induced height gain does occur, there is no good evidence that this will lead to improved psychosocial well-being.

The discussion with the parents should then address how a predicted change in height balances with the risks and burdens of treatment. Although treatment-related risks from GH are low, long-term follow-up studies have revealed conflicting data regarding potential increased morbidity and mortality in young adults who were previously treated with GH.^{20,21} Thus, the family should be informed about endocrinologists’ consensus that an ongoing study of potential post-GH treatment metabolic or cancer risks is needed and is underway.²² Safety is a relative concept. For children who are short but otherwise healthy, even a small risk for a long-term adverse effect may not be outweighed by an uncertain chance at some benefit. When treatments are not crucial for maintenance or restoration of health, these considerations become paramount. Although injection discomfort and resistance are not usually major issues for 14-year-old GH recipients, this particular child might well experience significant anxiety about painful shots being given for reasons he does not understand.

In addition to the considerations of informed consent, physicians must also consider the cost. GH treatment of ISS still presents a cost burden (conservatively estimated at \$35 000–\$50 000 per inch of height gained; in some cases, each inch could cost \$90 000). The physician has a duty to use health care resources responsibly, whether paid for by private, public, or personal funds. Those in the clinical vignette presumably assume that third-party support for GH treatment of ISS is available, although such support is decreasing in many areas.

Given all these considerations, I recommend evidence-based counseling that includes the following 3 crucial points: (1) your child’s height is most likely not the primary factor affecting his or her

psychological well-being, (2) GH treatment will improve the growth rate and may modestly increase height attainment but has not been shown to predictably improve psychosocial well-being, and (3) it is, therefore, uncertain whether or to what degree the benefits of treatment outweigh the risks, however small, for your son.²³ Given the numerous factors portending a relatively poor response to GH for this child, my inclination would be toward nontreatment along with reassurance that such a decision would not signify a meaningful “lost opportunity” for height gain or quality of life improvement. My experience has been that many parents, through engaging in such a discussion, reach a similar conclusion.

That being said, I would acknowledge that disordered growth, like disfiguring physical traits, can be disabling and that treatment, even if only partially effective, is within the range of appropriate medical choices. To respect the ethical principle that similar cases (of extreme short stature) should have similar access to approved treatment and acknowledging that cognitive impairment should not by itself preclude GH treatment, I would allow and supervise growth promotion treatment if the family, informed as above and contrary to my recommendation, still felt strongly that such therapy was in their child’s best interest.

**DAVID E. SANDBERG, PHD, AND
MELISSA GARDNER, MA, COMMENT**

Aside from cases in which a documented GHD exists, decisions for or against GH therapy are complex. They involve consideration of patient and family values balanced with a growing, but as-yet incomplete, research literature on the predicted growth effects of GH in individuals exhibiting syndromic features. Therefore, in response to the

parents' question of "What would you do?" I would refrain from providing a recommendation for or against GH therapy, and instead, engage the family in shared decision-making (SDM).

SDM refers to a process by which providers and patients and/or families collaboratively arrive at clinical management decisions on the basis of clinical evidence that balances risks and expected benefits with patient and/or family preferences and values.^{24,25}

SDM requires recognizing that a decision is required, knowing and understanding the best available evidence, and incorporating the patient's (and, in pediatrics, the parents') values and preferences into the decision.²⁶

The first step is to carefully explore with the family what they already know and expect would happen if he began receiving GH. Specifically, we would ask the parents what they want for their child. Of note, a number of characteristics were presented in the case description (short stature, craniofacial anomalies, hearing loss, developmental delay associated with supportive educational services, and an anticipated minimal capacity to live independently as an adult). We would ask the parents how they imagine their son's physical, psychological, cognitive and/or academic, and social functioning will be affected by GH and to consider how these effects may play out in the near-term and in their son's future. To the degree that he can participate, I would similarly learn what the adolescent boy wants and expects.

We would then stress to the parents that there are 2 aspects of GH treatment to consider, as follows: the end goal and the process by which this is achieved. We would ask them to consider and discuss how the process of GH administration may affect this youth and this family. Conceptualized as

"treatment burden" or "spillover effects,"²⁷ the act of daily injections and regular visits to endocrinology specialists that emphasize growth may negatively affect patients' self-perceptions.²⁸ Other possible burdens to the family include travel costs, time away from school and jobs, and financing the treatment (including copays and deductibles for the GH itself and clinic visits). Estimated annual cost of GH for ISS is between \$35 000 and \$90 000 per inch²⁹ (the wide disparity in cost estimates reflects the wide range of possible outcomes with treatment) and results, in terms of projected height gain, are difficult to predict.³⁰

Because the average height gain over predicted adult height is 4 to 5 cm, GH treatment would allow this youth to be 62.5 or 63 in rather than 61 in tall as an adult. How might this increase in height affect him? There are no good studies that might shed light on the potential benefits of GH treatment on such end points.

Of note, the presumptive diagnosis is ISS, yet this boy also exhibits craniofacial anomalies, and it is suspected that an as-yet undiagnosed genetic variation may account for syndromic features. This increases the uncertainty of any predictions because his chronological age, bone age, and tempo of puberty will all be different from children without his suspected but as-yet undiagnosed genetic syndrome.³¹

The final phases of the SDM process require examining to what degree the evidence fits with expectations and values of the patient, the family, and the doctors.³² Before coming to a conclusion, assess, alongside the family, their understanding of the different options and possibilities to address their concerns about the adolescent's growth (consider social and psychological services in addition to or in place of GH treatment), their understanding of the research evidence that speaks to their beliefs about and hopes

for GH treatment as it relates to their son, and their understanding of known risks, benefits, and areas of uncertainty. Finally, assess the degree to which each individual feels ready to make a decision regarding GH treatment.

In conclusion, it is understandable that parents often expect clinicians to provide definitive recommendations for or against treatment. However, this approach is not recommended with regard to decisions about GH treatment in patients who are not GH deficient. We advocate reframing the discussion from "what does the doctor say we should do" to engaging the family in a process of SDM in which they play an active and vital role.

JOHN D. LANTOS, MD, COMMENTS

GH therapy has been ethically controversial for over 30 years. The reason is clear. Short stature is not a disease, but it does have psychosocial sequelae. But those only occur because of relative short stature. If everyone was 5 ft tall, nobody would be stigmatized for being 5 ft tall. Stigma arises only because other people are taller. Thus, the treatment of any 1 person makes sense only because it evens the playing field and confers benefits that are relative to the patient's ultimate place in the population growth distribution.

In addition, GH therapy is associated with a perfect storm of ethically complicating factors. The treatment is expensive. The proper boundaries of treatment are based on variables that are continuous rather than dichotomous. The treatment is long-term and burdensome. The effect of treatment is only minimal and highly uncertain.

To see how all of these factors play out, consider the following thought experiment: imagine that, for the child in this case, a single dose of an inexpensive, safe, pleasant-tasting

liquid medication could reliably increase his final adult height by 3 in. I think the decision about whether to give it would be easier. Even then, however, it wouldn't be obvious. Doctors and parents would still need to consider the goals of treatment. The underlying issue (highlighted by the thought experiment) is that even if cost, burden, and uncertainty of outcome were not factors, we would still face the central question about the goals of treatment for both this patient and for children in general. The psychosocial advantages and disadvantages associated with one's stature are necessarily related to one's relative stature in comparison with others. This unique dilemma is inherent in GH treatment. We are always treating both an individual with a potentially disabling condition and, at the same time, a societal injustice that arises from the stigma associated with short stature. The dilemmas associated with these dual goals will never go away.

All of the cases in Ethics Rounds are based on real events. Some incorporate elements of a number of different cases in order to better highlight a specific ethical dilemma.

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ABBREVIATIONS

GH: growth hormone
 GHD: growth hormone deficiency
 ISS: idiopathic short stature
 SDM: shared decision-making

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