

Virtual Mentor

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Clinical Case

Treating Short Stature with Growth Hormone

Commentaries by Melissa D. Colman, MA, and David E. Sandberg, PhD;
by David B. Allen, MD; and by Wilma C. Rossi, MD, MBe

Mr and Mrs Malcolm are worried about the growth of their 5-year-old son, David. David was the shortest child in his preschool classes, and his parents worry that, as he enters kindergarten, he may be teased for his shortness. Looking ahead, they fear all kinds of other consequences; competitive sports could be closed to him, and dating and job finding could be more difficult than for his taller contemporaries. Mrs Malcolm is 5 ft tall, and Mr Malcolm is 5 ft 4 in. They have expressed their concerns over the course of David's last few pediatrician visits. The pediatrician, noting in David's chart that he has been approximately 3 standard deviations below the mean for height since 18 months of age, refers the Malcolms to Dr Tyson, a pediatric endocrinologist.

Dr Tyson orders several tests to determine whether David's short stature is due to an underlying pathology (eg, Turner's syndrome, renal insufficiency) or growth hormone deficiency. All tests come back negative. After a radiological evaluation, Dr Tyson concludes that David has idiopathic short stature (ISS), specifically, familial short stature; he is short because his parents are short. The Malcolms are relieved that David does not have a serious illness, but their fears and concerns are not abated by Dr Tyson's diagnosis. Mr Malcolm recalls the pain of being a short teen and still feels that people look at him awkwardly when they first meet him. A lawyer, he prefers to do most of his initial client interviews by telephone. Mrs Malcolm doesn't want her son to be shorter than girls his own age, and she fears that he could be psychologically scarred as he gets closer to puberty.

The Malcolms tell Dr Tyson that they have read on the Internet that human growth hormone therapy (hGH) is safe and effective for children like their son. They are eager to get David's therapy started as soon as possible and ask Dr Tyson to prescribe the treatment for him. When Dr Tyson begins to tell them that most insurance companies do not cover GH therapy for ISS cases, Mr Malcolm declares that they have decided to look at the therapy as an investment in David's future, as important as private school education, if not more so.

Commentary 1

by Melissa D. Colman, MA, and David E. Sandberg, PhD

The Malcolms' worries about David's future are understandable in view of the stereotypes about negative experiences of individuals with short stature [1]. The Malcolms believe their son can be spared these problems if he receives growth

hormone (GH) therapy. With the possible exceptions of growth hormone deficiency (GHD) and Prader-Willi syndrome, for which metabolic benefits of GH therapy have been documented, the primary rationale for GH treatment has been that extreme short stature constitutes a physical disability and creates a significant psychosocial burden [2-5]. Thus treatment is predicated on the belief that GH-induced increases in height will improve the short individual's quality of life. The abundance of synthetic GH and uncertainty regarding the diagnosis of GHD [6], contribute to the controversy over who should receive treatment. Allen and Fost infer from the growing number of conditions for which GH is prescribed that "the cause of short stature is not morally relevant in deciding who is entitled to treatment" [7]. Instead, they argue that GH therapy is indicated not by virtue of a medical diagnosis but whenever a *disability* in adaptation can be attributable to short stature. Therapy should be aimed, they say, at correcting this disability through treatment up to the point that an adult height within the "normal range," ie, the 5th percentile, is attained.

Benefits versus Risks

It is assumed that GH-induced increases in stature will improve child and adolescent psychosocial adaptation and adult quality of life. Growth benefits of GH treatment for idiopathic short stature, although reliable, are modest, with an average of 4 to 6 cm gained in adult height [8]. Accordingly, many individuals with ISS remain shorter than average even with treatment. Although clinic-based studies corroborate impressions that short stature is associated with psychosocial stresses like teasing and juvenilization (ie, the tendency to misperceive the individual's age and to treat that person as younger than his or her chronological age) these same studies fail to demonstrate that the experiences are associated with psychological dysfunction [9-11]. Moreover, the relationship between negative social experiences and psychosocial adaptation was weaker than the influence of demographic variables such as parental education and marital status [9].

If youths who are shorter than average, even markedly so, are psychologically as well-adjusted as those of average height, detecting psychological benefits of GH-induced increases in growth becomes a dubious pursuit. In fact, no rigorously designed studies provide evidence demonstrating that GH treatment leads to improved psychosocial adaptation in individuals with ISS [12, 13].

With regard to safety of GH, only short-term data are available for individuals receiving the doses approved by the FDA for ISS. The possibility of unforeseen risks in treating children with pharmacologic doses of recombinant human growth hormone (rhGH) [14] is particularly important to parents who report that their main concern about rhGH treatment pertains to its risks [15]. As recently noted in an editorial following the publication of 2 industry-sponsored GH safety studies in ISS [16, 17], Cuttler stated that because ISS, by definition, occurs in otherwise healthy children, decision making must consider the morbidity of the untreated state and the anticipated treatment benefits [18]. If the goal of GH therapy is to maintain positive psychosocial adaptation, then evidence must first be provided that short stature is associated with significant problems for the individual and, secondly, that hormone-

induced increases in growth ameliorate this situation. As already noted, evidence in support of these assumptions is nonexistent.

Age as a Factor in Clinical Decision Making

At 5 years of age, David lacks the ability to give informed assent to GH therapy; rather, his parents' decisions and their informed consent to medical care are substitutes [19]. To be effective at increasing rate of growth or final adult height, GH administration is typically recommended during childhood before bone epiphyses have fused and growth is no longer possible. Hence treatment would need to begin before David is old enough to give either informed consent or assent.

It has been argued that GH treatment of ISS is largely a cosmetic procedure aimed at augmenting or enhancing health or beauty [20, 21]. This claim prompts us to ask whether parents—who have great influence in shaping their child's values, beliefs, and education—should be given the right to extend their decision-making role to physical manipulation of their child's appearance via a lengthy and burdensome medical intervention?

Information to Provide to Parents

Good ethics are predicated on good facts, and, in this instance, it is necessary to provide David's parents with those facts. This can be accomplished by addressing Mr and Mrs Malcolm's specific concerns.

Teasing. Some children with short stature do report being teased, but few report difficult psychosocial adaptation as a result of that teasing. Teasing is a normal childhood phenomenon [22] and should not, by itself, be considered a predictor of undesirable outcomes. Also, because growth-promoting benefits of GH treatment are modest and variable, it would be a mistake to assume that height-related teasing will cease with treatment. David's predicted height, based on his parents' average height, is below the mean for adult males, and, even with treatment, David is likely to remain one of the shorter children in his class.

Competitive sports will be closed to him. Indeed, David's size may limit his participation and success in some sports. However, we do not know how important sports are to him now, or if they will be in the future. In the event that he comes to value sports, a variety of sports exist where size is not necessarily a predictor of success (eg, swimming, diving, golf, soccer) and there are some where short stature may even be an advantage (eg, gymnastics, equestrianism).

Job finding will be difficult. Laboratory studies suggest that people hold stereotypic beliefs that shorter people earn less or are afforded less respect; however, when research is brought out of the lab and into the "real world," the effect is diminished and open to other, nonsocial interpretations [1, 23]. In this case, Mr Malcolm appears to have a successful law practice and has found a way to cope with his perceived difficulties.

David will be shorter than girls his age and dating will be difficult. Throughout childhood girls are normally taller than boys because girls enter puberty and achieve their "growth

spurt” earlier than boys. The adult sex dimorphism in height (of approximately 5 inches) is related to the later onset of male puberty [24].

With regard to heterosexual dating and partner selection, although a taller male preference exists, this does not preclude shorter men from dating or marriage. Again, there is a laboratory versus real-world difference. For example, Hensley found evidence that, when asked what about the height of an “ideal partner,” women preferred taller men and men preferred shorter women; however, the magnitude of this preference was reduced when men and women were asked to report their own heights and that of their current partners [25]. Hensley concluded that shorter men are not necessarily disadvantaged; David’s parents are another case in point. Moreover, given that, in the general population, men are taller than women by an average of 5 inches, David, with a mid-parental target height of 5 ft 5 in, would be taller than about half of adult women.

Enhancement Medicine

It can be argued that short stature, unless proven otherwise in the individual case, is a matter of normal variation. The FDA-approved indication of GH treatment for ISS qualifies individuals more than 2.25 standard deviations below the mean for age and sex, or the shortest 1.2 percent of children. If all children under the first percentile received GH therapy, this would shift the mean height and create a new population of those below the first percentile, who would then be eligible to receive treatment and would create a new population below the first percentile, and so on and so on.

One factor that might prevent this “creeping norm” from occurring is cost. Cost does not appear to be an issue for the Malcolm family, so it will not be addressed here other than to say that, given the expense of this treatment regimen (the annual cost for 1 child weighing 30 kg is approximately \$15 000 to \$20 000 [7] with higher pubertal doses that can exceed \$50 000 per year [26]), it is largely inaccessible to any family for whom it is not covered by health insurance. On the societal level, this would have the effect of selectively distributing short stature to the less wealthy or uninsured [19, 27].

Role for the Pediatric Endocrinologist

David’s parents came in with a diagnosis, prognosis, and treatment plan in mind: that their son (1) has short stature, (2) will suffer from psychosocial problems similar to those of his father who attributes his problems to his own short stature, and (3) needs GH injections so that he is no longer “short” and will, therefore, not experience the associated psychosocial problems. This declaration places the physician in an uncomfortable situation—the parents are asking the physician to rely entirely on their report and treat a psychosocial problem (that is not currently in evidence) with a lengthy pharmacological treatment for which informed assent from the child cannot be obtained.

Pediatric endocrinologists and other health care professionals can be instrumental in countering negative stereotypes attributed to short stature as well as allaying parental concerns which are unfounded and which may be interpreted by a child as evidence that there is something “wrong” with him or her. The physician might recommend

counseling for the Malcolms to discuss their unrealistic expectations about the auxologic benefits of GH treatment in GH-sufficient youth [8]. They would also be reassured that, based on the empirical literature, short stature need not limit David's range of interests, experiences, or accomplishments. Should problems emerge, discussions of ways to cope with those problems, possibly with the assistance of a pediatric psychologist, can be helpful. Recommending that the family seek counseling may make the Malcolms feel as though they have not been heard; that the pediatric endocrinologist is recommending a psychosocial treatment for a problem they define as physical/medical. However, the converse is also true: focusing solely on the physical, medical, and pharmacological aspects limits treatment options for addressing the psychosocial adaptation problems, if, in fact, they occur.

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Commentary 2

by David B. Allen, MD

Ten years ago in the US, growth hormone (GH) therapy was approved only for GH deficiency, and its scarcity provided a barrier to expanding its use beyond children who were unequivocally GH deficient. Today, human growth hormone (hGH) is approved by the FDA for treatment of short stature due to Turner's syndrome, chronic renal insufficiency, intrauterine growth retardation, Prader-Willi syndrome, and severe familial or idiopathic short stature. GH is now synthesized in unlimited amounts, and the increased supply has been matched by growing demand. The consensus in the medical community is that the etiology of short stature is no longer morally relevant in deciding who is entitled to treatment. More than 40 000 US children are currently receiving treatment at a cost of between \$5000–\$40 000 per year to “correct” their short stature. Prescribing decisions therefore require balancing responsible use of costly medical resources with an obligation to do what is best for each patient.

This case highlights key ethical conundrums involved in access to GH therapy: (1) Does severe short stature in this child constitute a disability that is deserving of medical intervention? (2) What information should be provided regarding benefits, risks, and costs? (3) Is it advisable to wait until David is old enough to give assent or informed consent? (4) Should public funds or private insurance support such treatment, and, if so, how do we decide the height at which David is no longer “disabled” and further treatment would be enhancement?

As illustrated by this vignette, concerns about psychological harm during childhood and adulthood are invoked as the primary rationale for treating short stature. Based on the assumption that there is a link between stature and disability, the normal, short child's valid concern is identical to that of the growth hormone-deficient (GHD) child; namely, “I am short and I would like to be taller.” To child and parent, it is irrelevant whether the condition is a well-characterized “disease” caused by GHD, or a less understood process, as is the case in Turner's syndrome and idiopathic short stature. If “enhancement” refers to a desire for a child to be taller than he would be if left alone, then all children involved in this debate about access to GH are seeking enhancement.

But is short stature really the disability it has been made out to be? If the ultimate goal of GH therapy is improved quality of life by virtue of greater height, documentation of psychosocial impairment due to stature ought to play an important role in the initiation of GH therapy and evaluation of its efficacy. Data confirming this long-held assumption, however, are actually scarce. For instance, a recent community-based study of middle school children (many of whom were in the <5th percentile for height) failed to show a relationship between childhood short stature and psychological morbidity or reputation among peers [1]. In other words, short stature was not shown to be a predictable disability for most children.

Clearly, however, there are situations where treatment can be justified. In the case described here, a likely convergence of familial short stature and constitutional growth delay patterns can result in particularly extreme childhood short stature. The Malcolms can be told with confidence that GH therapy would likely accelerate David's growth and, within a few years, allow him to return to a normal childhood growth curve, though still at the lower height percentiles. Studies suggest that as much as 1 cm of

height per year of treatment can be added to final adult height, particularly if bone age is delayed at initiation, if treatment occurs primarily before puberty, and higher doses are used. In cases like this, where the short stature is primarily genetic and the ability to delay bone age is minimal, prediction about additions to adult height should be more conservative.

Since duration of treatment is a key predictor in ultimate increment in height, the option of waiting until the child gives assent to daily injections would diminish the response. In fact, shifting treatment years from pre-puberty (~\$10 000/year) to puberty (~\$20–40 000/year) could also add to eventual costs. Nevertheless, thoughtful pediatricians raise concerns about the potential harm of labeling an otherwise healthy child as somehow unacceptable in society's and his parents' eyes. The potential adverse effect of being labeled "sick" or "disabled" and receiving daily medical treatment remains unproved in general but merits consideration for each individual child. Other risks of GH therapy appear very low—and thus seem to be balanced favorably by the perceived benefits [2]. However, families should know that: (1) this risk assessment needs to be constantly re-evaluated as dosages used in GH therapy are increased and, (2) safety surveillance represents 20 years of experience, but not 40-60 years.

Aside from responsibly allocating health care resources, those prescribing GH must address what is truly known about the hoped-for benefit—an improved psychosocial outlook resulting from increased height. No one doubts the basic premise that there are measurable benefits in social and economic success associated with taller stature in our society. But the assumption that GH therapy can achieve these same results for short children has not been demonstrated. For example, in a recent study of patients with Turner's syndrome (TS), height at the conclusion of GH therapy did not contribute substantively to quality of life [3]. Given the other health problems confronting women with TS, these findings may not apply to other groups with short stature. On the other hand, one could argue that demonstration of a measurable benefit in quality of life should be required to justify subsidized, expensive, invasive, and long-term GH therapy for children who are otherwise healthy. To date, however, growth rate and final adult height remain the primary measures by which therapeutic success is judged by physicians and insurance providers alike.

When to Stop Treatment

Determining an appropriate end-point for GH therapy remains a challenging ethical issue. The recent FDA approval for GH treatment of children with idiopathic short stature (ISS) includes a threshold for initiation (<first percentile), but provides no guidelines for termination of treatment. Attainment of an individual's predicted maximum potential for height (wherever that may fall in the adult range of height) remains a goal for many. On the other hand, if the rationale for GH therapy is alleviation of "disabling" short stature, the logical definition of therapeutic success would be an adult height no longer considered a disability. Children with extreme short stature of any cause have a rightful claim to effective treatment to become taller, but they cannot make a strong claim to be taller than others who are within the normal range and therefore are not entitled to treatment. This is not changed if parents decide

that an appropriate height for their children is taller than normal. It is difficult to justify use of private or public insurance funds to make some people taller than those in the lower range of the normal distribution. Parental expectations should not determine what treatments are subsidized, but, as implied in this case, if parents want to purchase more GH on their own to buy additional height for their son, there isn't a strong argument for preventing them from doing so.

Until evidence supports that GH treatment for short stature has some value in improving quality of life, access will be guided by predicted adult height as a surrogate outcome. Clearly, however, pressure from payers to provide quality-of-life evidence will increase. While no policy for GH therapy will eliminate those in the first percentile, a coherent policy framework would focus on bringing children into the height that confers a *range of normal opportunity* without further enhancing those who will achieve or have achieved a height within the normal adult distribution. By adhering to *treatment* of disabling short stature and resisting the *enhancement* of normal stature, physicians treating children with GH would minimize their contribution to society's perception that to be taller is to be better.

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Suggested Reading

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Commentary 3

by Wilma C. Rossi, MD, MBe

FDA approval for growth hormone (GH) therapy for individuals with idiopathic short stature (ISS) has made cases like this one commonplace for pediatric endocrinologists.

GH treatment has received much media attention, and parents are exploring it as an option to increase stature in their short children with no medically recognized growth deficiency. In considering GH treatment of a normal child, Dr Tyson faces some ethical dilemmas. The first is efficacy. Pediatric endocrinologists disagree as to whether or not GH treatment actually increases growth in ISS and results in taller adult stature. Dr Tyson is obligated to evaluate the literature critically to determine whether GH will be an effective treatment for this patient. If not, he should not prescribe it. A frequently quoted study funded by the pharmaceutical industry demonstrated that short-statured normal children on GH ultimately achieve adult heights that are an average of 5 cm taller for boys and 5.9 cm taller for girls than their predicted adult height without the hormone [1]. This represents a minimal increase in height; these children were still short as adults. Of note, a group of children in this study did not increase their adult height at all after having been subjected to daily GH injections for an average of 5.5-6 years [1]. Critical review of this study shows that the group of children with low insulin growth factor-1 (IGF-1) levels grew better on GH than those with normal levels whose adult height did not increase. In this instance it is likely that GH was effectively treating a biochemical abnormality.

Assuming that Dr Tyson thinks that David is likely to be taller if he is treated with GH, the second ethical point to consider is the risk/benefit ratio of this treatment in patients with ISS. When used for other indications, GH appears to be safe. The metabolic consequences of GH used in ISS has been studied (again with pharmaceutical company support) with no adverse effects reported after 5 years [2]. However, since no long-term studies have been done, the potential for unforeseen complications exists. Psychological factors to consider include trauma associated with daily injections; treatment may also reinforce a negative self-image or generate a perception that short stature is a disease or disability [3].

What are the benefits of effective treatment? Severe short stature can pose physical limitations in a world that is geared to the average-sized individual. Driving a car or working at standard height desks and counters can be a challenge for the very short adult. Mr and Mrs Malcolm are convinced that short stature is associated with many other disadvantages, and Mr Malcolm attributes his own difficult social interactions to his short stature. The couple is concerned that David will be psychologically scarred by his short stature and assumes that GH treatment leading to taller stature will improve his psychosocial well-being. Although this notion has been a widely held, current data indicate that the psychological functioning of children and adults with short stature is indistinguishable from that of their peers. Moreover, studies do not support the claim that quality of life is improved after GH therapy [4, 5].

Dr Tyson should also consider whether providing David with GH is therapy or enhancement. GH therapy is routinely prescribed for children with GH deficiency, where there are few ethical dilemmas because GH is being used to treat a disease or disorder. Children with Turner's syndrome and renal insufficiency are not GH-deficient, but since they grow better on GH it is routinely prescribed as part of standard therapy in these conditions. The therapy/enhancement question is a tough one because children with ISS, though "normal," are as short when they are adults as

those with GH deficiency, Turner's syndrome, and renal insufficiency. Consequently, it seems reasonable to establish a minimum adult height below which one experiences physical limitations and, from there, to say any child who is unlikely to achieve a height above this minimum should be a candidate for GH therapy, regardless of diagnosis. The FDA arbitrarily approved GH for treatment in ISS of children whose predicted adult height fell below the first percentile, ie, lower than the height of 1 percent of adults. However, the height below which short stature is a true disability has not been determined and should be investigated. Moreover, the goal of treatment should be to achieve a normal adult height, not the maximum height that an individual can obtain. Once a child reaches a height at which his or her projected adult height is no longer associated with disability, GH should be discontinued. This approach attempts to prevent disability and normalize—rather than enhance—stature [6].

Social Inequities

Matters relating to social justice should not be overlooked in the ethical analysis of GH treatment of short stature. The economic consequences of such treatment are significant. The annual cost of treatment of all children whose height falls below the first percentile for any reason including ISS, approaches \$4 billion [6]. When millions of Americans have no access to health care, should making healthy children taller be a priority? Currently, few insurers pay for GH treatment of ISS. But if society continues to medicalize short stature, insurers may be forced to pay for GH for all short children. For now, GH treatment for ISS is essentially available only to those, who, like the Malcolms, can afford to pay for it. If this inequality in access to GH were to continue, the already disadvantaged poor would become the shortest members of society.

Looking at the big picture, it's true that no matter how effective and accessible GH therapy is, someone will always be the shortest. By recommending GH treatment for ISS, society sends the message that taller is better and endorses prejudice against whoever is shortest—no matter what his or her actual height is.

After careful review of the medical and ethical issues involved in this case, Dr Tyson might assess this case as follows. David meets the FDA indication for GH therapy in ISS since his predicted adult height falls below the first percentile. A review of the literature suggests that it is unlikely that GH will benefit David since his tests, including IGF-1, are completely normal. Even if it were to benefit him, the expected increase in his height would be minimal, and he would still be a short adult. Current data does not support the theory that short stature impacts psychosocial well-being and, although the short-term risks of GH appear low, long-term risks are unknown. David may perceive that treatment of his short stature indicates that he has a serious disability, and this may reinforce a negative self-image regarding his stature. On a societal level, Dr Tyson must also consider the cost of treatment, unequal access to GH, and the “medicalization” of short stature. Weighing the potential risks—both social and medical—against the lack of evidence that David will either grow significantly taller or have improved quality of life if he does attain taller stature, Dr Tyson can confidently conclude that GH treatment is not warranted.

How do I honestly think Dr Tyson will fare in this matter? He will present all of this information to Mr and Mrs Malcolm who will still be adamant that their son be treated with GH even if there is only a small chance that it might make him taller. Dr Tyson will suggest that they monitor David's growth and re-evaluate him in 1 year and agree that he will continue to review the medical literature regarding treatment of ISS and notify the Malcolms of any new information. The Malcolms will leave the office, obviously unhappy with Dr Tyson's recommendations. The next day they will call and request that David's records be forwarded to another pediatric endocrinologist whom they will consult for a second opinion.

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