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A comparison of referral patterns to the pediatric endocrine clinic before and after FDA approval of growth hormone for idiopathic short stature

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Abstract

Background—Short stature is a common reason for referral to the pediatric endocrine clinic. In 2003, the US Food and Drug Administration (FDA) approved the use of growth hormone (GH) for the treatment of children with idiopathic short stature (ISS).

Objective—To explore if this indication changed referrals for short stature (SS).

Design/Methods—A retrospective chart review of children seen for SS in the pediatric endocrine clinic between July 1998 and June 1999 (interval one, n=138) and July 2005–June 2006 (interval two, n=268) was performed. Variables collected included age, gender, height (h), and parental heights.

Results—Average height standard deviation score (HT-SDS) was -2.11 ± 0.9 in interval one and -2.14 ± 0.83 in interval two ($p=ns$). No differences in age, gender distribution, relationship between child and parental heights, the proportion of subjects started on GH for ISS or in the HT-SDS of those treated between the two intervals were identified. Nearly half of all children referred in each interval did not meet the technical criteria for short stature.

Conclusions—No differences in referral patterns for SS in our area following FDA approval of GH for ISS were identified. Although referrals appear unchanged, additional investigation of GH prescribing patterns before and after this new indication is needed. Continued education of primary care physicians and the general public regarding the definition of SS and the eligibility for GH therapy should be pursued.

Keywords

growth hormone; idiopathic short stature

Introduction

Approximately 40% of new patient referrals to the pediatric endocrine clinic are for short stature (1). In addition, many families present with the explicit question of whether growth hormone (GH) therapy should be administered to their child (2). The increased awareness of exogenous GH treatment probably stems from the 2003 US Food and Drug Administration (FDA) approval of GH for otherwise healthy children with idiopathic short stature (ISS), defined as a height of -2.25 standard deviation (SD) and growth rates unlikely to attain 1.6 m in boys and 1.5 m in girls (3). This is the shortest 1.2% of children. In recent years, we have had the anecdotal impression that increasing numbers of children being referred for short stature have heights that are well within the normal range. Whether this has actually been the case was unknown. Therefore, we undertook a systematic analysis of short stature referrals to our clinic before and after FDA approval of GH for ISS.

Methods

Following institutional review board approval, medical records of children referred to the pediatric endocrine clinic at Riley Hospital for Children for short stature during two 1-year periods were reviewed. The first interval was from 1 July 1998 to 30 June 1999, and the second was from 1 July 2005 to 30 June 2006. During this time span, our section has grown from five (during interval one) to 10 (during interval two) full-time pediatric endocrinologists with a referral base of approximately 5 million from Indiana and surrounding states. Variables collected from the initial visit included gender, age, height (height), and parental heights. We also ascertained whether GH stimulation testing had been performed, whether GH had been prescribed, and if so, for what indication. GH stimulation testing was performed with arginine and clonidine with a normal response defined as peak GH level of 10 ng/mL or greater in the earlier period and 5 ng/mL or greater in the later period. The normal peak value decreased owing to a change in the laboratory assay. Children <2 years of age were excluded. The descriptive statistics of the sample and the outcome measures were calculated. The Student t-test was used to compare the two groups. The χ^2 -test was used to compare proportions. All calculations were performed in SPSS version 16.0 (SPSS Incorporate, Chicago, IL, USA). A p-value of 0.05 was considered statistically significant. Data are expressed as mean $\pm$ standard deviation.

Results

In interval one, 138 subjects (90 boys) aged 9.15 ± 4.48 years were identified. In interval two, 268 subjects (171 boys) aged 9.51 ± 4.45 years were identified. No differences in age or gender distribution between intervals were found. Average height standard deviation score (HT-SDS) in the recent time period was -2.14 ± 0.83 , which was unchanged from the earlier interval, in which it was -2.11 ± 0.9 . The percentage of patients who did not technically meet the definition of short stature (height <-2 SD) was 43.1% in interval one and 43.8% in interval two. Of these, 23 subjects (16.6%) in interval one had a height less than the fifth percentile but greater than -2 SD, whereas 47 subjects (17.5%) in interval two were in this category. The distribution of HT-SDS between the two intervals was similar, as shown in Figure 1. Similarly, no differences between intervals were found in either target height

(THT) SDS or child HT-SDS and THT SDS. Baseline characteristics for all new referrals for short stature in both time intervals are summarized in Table 1.

In interval one, 32 out of 138 subjects (23%) underwent GH stimulation testing. Of these, 14 were determined to have ISS and had an average HT-SDS of -2.59 ± 0.65 . Of these, four (two males and two females) were started on GH therapy for the indication of ISS. The average HT-SDS in those started on GH therapy was -2.5 ± 0.49 . One subject had a HT-SDS of -1.8 which did not meet criteria for ISS. In interval two, 29 out of 268 subjects (11%) underwent GH stimulation testing of whom 17 were diagnosed with ISS with an average HT-SDS of -2.77 ± 0.7 . Of these, five (three males and two females) were started on GH therapy for the indication of ISS. Two additional boys were started on GH therapy without GH stimulation testing. The average HT-SDS for those started on GH therapy was -2.8 ± 0.83 . One subject had a HT-SDS of -2.01 which did not meet criteria for ISS. There was no difference in HT-SDS or the proportion of subjects started on GH therapy for ISS between the two time periods. Data regarding patients who were tested for GH deficiency and who were prescribed GH for ISS are summarized in Table 2.

Discussion

The use of GH for otherwise healthy short children has generated significant controversy based on ethical, social, moral, and economic grounds (4–6). Recent media coverage (7, 8) has raised concern that prescribing practices for GH therapy often do not follow FDA guidelines, and has resulted in allegations that physicians are promoting unnecessary and expensive treatment for cosmetic purposes alone. Even prior to FDA approval, published reports indicated that many non-GH-deficient children were being treated with GH therapy (9). However, to what extent referral and/or GH prescribing practices have changed since FDA approval of GH for ISS is largely unexplored.

In our study, no difference in referral patterns for SS before and after the indication for GH to treat ISS was found. The increase in sample size in interval two is commensurate with the growth in number of our faculty (and clinics) that occurred since the earlier time interval. An alternative explanation for this growth in sample size might be a heightened awareness of GH and its use by the medical and lay public. Similarly, prescribing practices were equivalent in the time periods analyzed and were conservative in both. Only one patient treated with GH for ISS in each of the two intervals had a HT-SDS greater than -2.25 . This is reassuring as it refutes claims of overzealous GH prescribing practices, at least at our large tertiary care center. Whether our findings would generalize to other regions of the country is unknown.

One troubling aspect of our study was that nearly half of the 439 children referred for short stature did not technically meet that definition. As has been previously reported (10), the preponderance of boys reflects a known referral bias based on greater perceived psychological difficulties in boys with short stature as compared with girls, although definitive evidence for a negative impact on quality of life is lacking (11, 12). It is certainly probable that some normal-statured children were appropriately referred owing to deceleration in height percentiles or other clinical features suggestive of a growth disorder.

However, the large number of children with heights >-2 SD and the frequent queries about GH implies significant misunderstanding on the part of parents and referring physicians. Family concern, physician demographic characteristics, and personal beliefs, and a child's growth pattern have all been shown to influence primary care provider referrals (13). Continued education directed at primary care providers and the general public regarding the definition of short stature and eligibility for GH therapy should be pursued.

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Figure 1.

(A) Distribution of height standard deviation scores of patients referred during interval one.

(B) Distribution of height standard deviation scores of patients referred during interval two.

Table 1

Baseline characteristics of children referred for short stature.

Variables	1998–1999 n=138	2005–2006 n=268	p-Value
Age, years	9.15±4.48	9.51±4.45	0.43
Gender	90 M: 48 F	171 M: 97 F	ns
Gender composition	65% M	63% M	ns
HT-SDS	−2.11±0.9	−2.14±0.83	0.74
% SDS >−2.0	43.1%	43.8%	0.81
<5th%, >−2 SD	23	47	0.83
THT-SDS	−0.31±0.85	−0.25±0.75	0.49
Child HT-SDS and THT-SDS	−1.74±1.27	−1.84±0.91	0.35

ns, not significant; M, male; F, female.

Table 2

GH stimulation and treatment data in the two intervals analyzed.

Variables	1998–1999 n=138	2005–2006 n=268	p-Value
Number of patients stimulated diagnosed with ISS	14	17	0.17
HT-SDS of ISS patients stimulated	−2.59±0.65	−2.77±0.7	0.19
Number started on GH for ISS	4 (2 M: 2 F)	7 (5 M: 2 F)	0.87
HT-SDS of patients started on treatment	−2.5±0.49	−2.8±0.83	0.79

M, male; F, female.