Medically Underserved Girls Receive Less Evaluation for Short Stature

WHAT'S KNOWN ON THIS SUBJECT: Boys outnumber girls ~2 to 1 in growth hormone (GH) registries and subspecialist endocrine clinics that evaluate short stature, yet the prevalence of growth-faltering in an urban pediatric primary care population was not related to gender.

WHAT THIS STUDY ADDS: Patterns in diagnostic testing of children with growth-faltering by their primary care pediatricians may lead to underdiagnosis of Turner syndrome and GH deficiency among girls.

abstract

OBJECTIVE: To determine if gender is associated with diagnostic evaluation by primary care pediatricians caring for children with growth-faltering.

PATIENTS AND METHODS: This was a retrospective study of children who were attending 4 urban pediatric primary care practices affiliated with a tertiary pediatric hospital. Growth-faltering was defined as height at the <5th percentile or a z-score decrease of ≥ 1.5 SDs before 18 months of age or ≥ 1 SD thereafter. For each child, height z score, age, gender, race, insurance, diagnostic tests, and subspecialist appointments were examined.

RESULTS: Of 33 476 children, 3007 had growth-faltering (mean height: -1.5 ± 1.0 vs 0.3 ± 0.9 SDs in those without growth-faltering). Boys comprised 53% of the growth-faltering group (vs 51% of the nonfaltering group; $P < .01$). Among children with growth-faltering, 2.8% had endocrinology appointments (vs 0.8% of others; $P < .0001$) and 6% had gastroenterology appointments (vs 1.5% of others; $P < .0001$). Subspecialty care was not associated with gender. Pediatricians ordered diagnostic tests for a significantly greater proportion of children with growth-faltering than others. In multivariate analysis of height z score among children with growth-faltering, tests for chromosomes (1.4% of short girls vs 0.4% of short boys; $P < .005$) and growth hormone/insulin-like growth factor axis (0.9% of short girls vs 1.8% of short boys; $P < .05$) were associated with gender. Thirty-five percent of the girls for whom chromosome testing was performed were 12 years old or older.

CONCLUSIONS: Patterns in diagnostic testing of children with growth-faltering by their pediatricians may lead to underdiagnosis of Turner syndrome and growth hormone deficiency among girls. *Pediatrics* 2011;127:696–702

AUTHORS: Adda Grimberg, MD,^a Kristen A. Feemster, MD, MPH,^{a,b} Susmita Pati, MD,^a Mark Ramos, BS,^a Robert Grundmeier, MD,^a Andrew J. Cucchiara, PhD,^c and Virginia A. Stallings, MD^a

^aDepartment of Pediatrics, ^bRobert Wood Johnson Clinical Scholars Program, and ^cClinical and Translational Research Center and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

KEY WORDS

growth-faltering, gender, race, pediatric primary care, diagnostic testing, subspecialist referrals

ABBREVIATIONS

GH—growth hormone

IGF—insulin-like growth factor

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Address correspondence to Adda Grimberg, MD, Division of Pediatric Endocrinology, Children's Hospital of Philadelphia, Room 11NW30, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104. E-mail: grimberg@email.chop.edu

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FINANCIAL DISCLOSURE: In the past 3 years, the Children's Hospital of Philadelphia Endocrine Division has been participating in the growth hormone registries of all the major growth hormone manufacturers (Eli Lilly, Genentech, Novo Nordisk, Pfizer, and Serono), and Dr Grimberg received honoraria and reimbursed travel expenses for presenting her research at growth hormone meetings sponsored by Pfizer and Novo Nordisk (but has never served on speaker bureaus); the other authors have indicated they have no financial relationships relevant to this article to disclose.

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In a retrospective review of children referred to a subspecialty growth center in 2001 for the evaluation of poor growth, we found that boys outnumbered girls 182 to 96. The referred girls were shorter than the referred boys relative to both the general population and their midparental target heights and were more likely to have an identifiable underlying disease.¹ In contrast, our subsequent study of 4 urban pediatric primary care practices in the same academic pediatric network revealed that the prevalence of growth-faltering was associated with younger age, white race, fewer primary care visits, and Medicaid insurance but not gender.² In this study we sought to focus on the management by primary care pediatricians of children with growth-faltering, specifically to examine the patterns of subspecialist referrals and diagnostic laboratory tests ordered and to determine if gender is associated with these patterns.

PATIENTS AND METHODS

Subjects, Height, and Covariate Data

The electronic health records (Epic-Care [Epic Systems Inc, Madison, WI]) of 33 476 children aged 6 months to 20 years who attended 4 urban pediatric primary care practices affiliated with a tertiary pediatric hospital from July 2002 to June 2005 were retrospectively reviewed, as previously reported.² Patient data, including height (or length, if age appropriate), age (at the first visit within the observation window that either met inclusion criteria for growth-faltering or, if none qualified, then the age at the first visit under observation), gender, race and ethnicity (National Institutes of Health and US Census Bureau system³), insurance provider (private, Medicaid, or self-pay), and primary care pediatrician gender, were extracted.

Growth-faltering was defined by clinical patterns that primary care pediatricians often use to signal a potential growth problem: (1) height at the <5th percentile ("below the curve" on the growth charts used) or (2) decrease in height z-score channel. To reduce the impact of physiologic rechanneling or measurement error on this study, the z-score decrease must exceed 1.5 SDs before 18 months of age or exceed 1.0 SD thereafter. To improve validity and reliability, growth data were excluded for children before 6 months of age, for low birth weight or premature infants before 2 years of age, and for outlying stature z scores beyond -5 or 3 SDs; these z scores likely represented biologically implausible values and were omitted as recommended by the World Health Organization and the Centers for Disease Control and Prevention.^{4,5} Two independent checks of data quality were performed as previously described.²

To obtain surrogate markers of family socioeconomic status, each patient who resided in Philadelphia County, Pennsylvania, was assigned to a residential census tract (ArcView 9.1 [ESRI, Inc, Redlands, CA]) as previously reported.² For the 28 656 patients whose addresses matched the census tracts, socioeconomic indicators were collected from 2000 US Census data.⁶ Each patient/family was assigned the median income, percentage employment over 16 years of age, and percentage of adult women and men of their respective census tracts with an education level greater than high school completion.

Outcome Measures

Electronic health records of all children with growth-faltering were reviewed for appointments during our 3-year window of observation. The number of encounters at their primary care clinics was tabulated, as were ap-

pointments in the subspecialty endocrinology and gastroenterology clinics at the affiliated tertiary care pediatric network. Diagnostic testing ordered by the primary care pediatricians was collected from the electronic health record and categorized. Rather than draw conclusions from unreliable data, we decided not to analyze diagnoses and focus only on the factors with consistently complete records. However, because Down syndrome is generally diagnosed by pediatricians during infancy more consistently than other syndromes, and it was such an obvious confounder for thyroid-function testing, we analyzed the laboratory testing with and without the children with Down syndrome and found that their inclusion/exclusion did not alter the results.

Statistical Analyses

Descriptive statistics were calculated by using JMP software (SAS Institute, Inc, Cary, NC) and are presented as means $\pm$ SD. Differences between means of continuous variables (such as height z score, age, and number of encounters) were compared by 2-sided *t* test and between frequencies of categorical variables (ie, gender, race, ethnicity, payer, and appointments or testing) by Pearson's χ^2 . Logistic regression analyses with effect Wald tests were performed to quantify the relationship between patient characteristics, specifically gender, and diagnostic tests ordered.

To quantify the relationship between patient characteristics including gender and subspecialist appointments, 1-way analysis of variance was used to assess univariate associations, and the GenMod procedure (SAS Institute, Inc) was used for multivariate analyses. Model results are presented as odds ratios with 95% confidence intervals and χ^2 *P* values. Median income was transformed into strata of \$10 000

to allow comparison of clinically significant differences in the models.

Human Subjects Considerations

This study commenced after approval by the institutional review board of the Children's Hospital of Philadelphia.

RESULTS

Subject Characteristics

These urban practices cared for predominantly black (87%) and Medicaid-insured (70%) children from low-income areas of Philadelphia. The children lived in census tracts with median household incomes of \$24 600 (interquartile range: \$20 600–\$28 800) and a median 29% of inhabitants below the federal poverty line (interquartile range: 21%–35%).²

Approximately 9% (3007) of the children had growth-faltering (mean height z score: -1.5 ± 1.0 vs 0.3 ± 0.9 SDs in those without faltering; $P < .0001$). Five hundred thirty-four children (1.6%) had height z scores below -2.25 SDs, which is the cutoff for the idiopathic short stature indication for GH therapy.⁷ The racial distribution of children with growth-faltering did not differ significantly between boys and girls, although a greater proportion of the short boys had Medicaid coverage.

Subspecialist Care

Only 8% of the children with growth-faltering received subspecialist care; 2.8% of children with and 0.8% of children without growth-faltering had an endocrinology appointment ($P < .0001$), and 6% and 1.5%, respectively ($P < .0001$), had a gastroenterology appointment (Fig 1). As seen in Tables 1 and 2, children with growth-faltering who received subspecialist care had greater deficits in stature and were followed more frequently in the primary care setting than the growth-faltering children who were not referred during this period of

FIGURE 1

Percentage of children with subspecialist appointments during our 3-year window of observation. Endo indicates endocrinology clinic; GI, gastroenterology, hepatology, and nutrition clinic.

observation. Subspecialty care was not significantly associated with gender. Although children who saw gastroenterologists were, on average, the same age as those who did not receive subspecialist care, children who saw endocrinologists were 2 to 3 years older. Black children were less likely to see a subspecialist than non-Hispanic white children, and the racial disparity was greater for endocrinology than gastroenterology appointments. Although Hispanic ethnicity was found more often among the growth-faltering children who received subspecialist care than those who did not, according to univariate analysis (Table 1), ethnicity was not a significant factor in any of the multivariate models of subspecialist care (Table 2), which suggests that the univariate association was a result of confounding by another variable.

Diagnostic Testing by Primary Care Pediatricians

Primary care pediatricians ordered diagnostic tests for a significantly greater proportion of children with than those without growth-faltering. For children in the group with growth-

faltering, pediatricians ordered a complete blood count for 60%, lead testing for 51%, hemoglobin testing for 16%, thyroid-function tests for 9%, liver-function tests for 6%, iron studies for 4%, bone age testing for 3%, celiac antibody testing for 1.7%, GH/insulin-like growth factor (IGF) axis-related tests for 1.4%, sweat tests for 0.9%, chromosome testing for 0.9%, sex hormone and/or gonadotropin testing for 0.8%, and metabolic studies for 0.4%.

Thyroid-function tests were the most frequently obtained endocrine-related laboratory study (9%). Because annual thyroid-function screening is standard of care for patients with Down syndrome⁸ and short stature is a feature of Down syndrome,⁹ thyroid testing for children with Down syndrome does not really constitute diagnostic evaluation of growth-faltering as it pertains to this study. After excluding children with Down syndrome from the analytic sample, thyroid-function tests remained the most frequently obtained endocrine-related diagnostic tests among children with growth-faltering (8%). To evaluate the possibility of an endocrine-related “diagnostic package” for growth-faltering, the frequency of the other diagnostic tests was analyzed as a function of concomitant thyroid-function testing. Among children without Down syndrome with growth-faltering who received thyroid-function tests, concomitant tests ranged from 23% (bone age) to 5% (chromosome testing) (data not shown).

In multivariate regression modeling of children with growth-faltering, height z score was significantly ($P < .05$) associated with complete blood count, tests related to diagnosis of HIV infection, liver-function tests, celiac antibody tests, other gastroenterology diagnostic testing, sweat testing, thyroid-function tests, bone age tests, GH/IGF axis-related tests, chromosome testing, and sex hormone/gonad-

TABLE 1 Characteristics of the Growth-Faltering Children Who Received Subspecialist Care (Univariate Analyses)

	Endocrinology (n = 61)	Gastroenterology (n = 156)	Both (n = 23)	Neither (n = 2767)	P, Univariate Analysis
Height z score, mean $\pm$ SD	-2.3 $\pm$ 0.8	-2.2 $\pm$ 1.0	-2.7 $\pm$ 1.1	-1.5 $\pm$ 1.0	<.0001
Female, %	41	50	43	47	.66
Age, mean $\pm$ SD, y	7.9 $\pm$ 5.3	4.9 $\pm$ 4.8	7.1 $\pm$ 5.2	4.9 $\pm$ 5.3	<.0001
Race, %					<.05
Black	69	76	78	83	—
White	20	14	13	9	—
Ethnicity, % Hispanic	3	4	4	1	<.05
Medicaid, %	71	73	78	74	.87
No. of PCP encounters, mean $\pm$ SD	3.1 $\pm$ 2.2	3.6 $\pm$ 3.6	3.7 $\pm$ 2.2	1.6 $\pm$ 1.2	<.0001
PCP gender, % male	21	17	26	22	.51
Income (\$1000), median $\pm$ SD ^a	25.7 $\pm$ 6.0	24.9 $\pm$ 7.6	30.1 $\pm$ 10.3	25.2 $\pm$ 7.4	<.05
Employment over 16 y, mean $\pm$ SD, % ^a	53 $\pm$ 6	53 $\pm$ 8	56 $\pm$ 8	53 $\pm$ 7	.37
Education beyond high school, mean $\pm$ SD, % ^a					
Female	41 $\pm$ 14	40 $\pm$ 15	47 $\pm$ 16	40 $\pm$ 15	.34
Male	35 $\pm$ 17	33 $\pm$ 16	35 $\pm$ 17	33 $\pm$ 16	.92

The data were analyzed by using 1-way analysis of variance. PCP indicates primary care pediatrician.

^a Census tract variable.

TABLE 2 Multivariate Analysis of the Growth-Faltering Children Who Received Subspecialist Care

	Endocrinology vs Neither		Gastroenterology vs Neither		Endo vs GI	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Height z score	0.59 (0.38–0.93)	<.05	0.76 (0.57–1.00)	.05	0.72 (0.39–1.34)	.31
Female	0.63 (0.28–1.42)	.27	1.35 (0.81–2.26)	.25	0.47 (0.16–1.37)	.16
Age	1.14 (1.07–1.22)	.0001	1.05 (1.00–1.10)	.06	1.14 (1.03–1.26)	<.05
Race (black vs white)	0.72 (0.19–2.74)	.63	0.54 (0.23–1.28)	.16	3.47 (0.56–21.5)	.18
Ethnicity (Hispanic)	1.31 (0.12–14.6)	.82	1.86 (0.44–7.89)	.40	0.10 (0.003–3.0)	.19
Medicaid	0.80 (0.33–1.96)	.63	0.99 (0.52–1.90)	.99	0.86 (0.26–2.82)	.81
No. of PCP encounters	1.64 (1.28–2.11)	<.0001	1.64 (1.41–1.91)	<.0001	1.00 (0.75–1.33)	.996
Median income (\$1000) ^a	0.84 (0.45–1.56)	.58	0.77 (0.51–1.16)	.21	0.91 (0.41–2.03)	.82
Employment over 16 y, % ^a	1.14 (0.72–1.81)	.57	1.19 (0.88–1.61)	.26	1.10 (0.62–1.89)	.79
Education beyond high school, % ^a						
Female	1.10 (0.69–1.72)	.71	0.87 (0.64–1.18)	.38	1.41 (0.81–2.48)	.23
Male	0.99 (0.62–1.57)	.95	1.05 (0.77–1.44)	.76	1.10 (0.58–1.99)	.82

PCP indicates primary care pediatrician.

^a Census tract variable.

otropin testing. Of these tests, 2 were significantly associated with gender: chromosome testing (1.4% of short girls vs 0.4% of short boys; $P < .005$) and GH/IGF axis testing (0.9% of short girls vs 1.8% of short boys; $P < .05$). Both tests were obtained for children who were shorter and followed more closely by their primary care pediatricians (Table 3). Similar to children with endocrinology appointments, children

who underwent GH/IGF axis testing were older than those who did not (Table 3). The age distribution of children with GH/IGF axis and chromosome testing is shown in Fig 2. It should be noted that 35% of the girls had chromosome testing at 12 years of age or older.

DISCUSSION

We found that growth-faltering was common in urban, largely minority, un-

derserved pediatric practices. Only 8% of the children with growth-faltering received subspecialist care (endocrinology or gastroenterology). It was notable that, compared with non-Hispanic white children, the black children were less likely to see a subspecialist, particularly an endocrinologist. Thus, the majority of children with growth-faltering were managed by their primary care pediatricians. Thyroid-function testing was the most frequently obtained endocrine-related diagnostic test. Pediatricians ordered GH/IGF axis tests twice as frequently for short boys than for short girls and chromosome testing for only 1.4% of the short girls.

A significant gender disparity was found in the proportion of growth-faltering children whose pediatricians ordered GH/IGF axis testing; the rate for boys was double that for girls. Both the children receiving GH/IGF testing and those with endocrine appointments tended to be older than the rest of the growth-faltering population. Taken together, these findings suggest that diagnosis of GH deficiency can be delayed or missed, especially among girls. Prompt diagnosis is needed for the timely initiation of GH therapy, which is critical for final height outcome.¹⁰ The importance of GH for cardiovascular,¹¹ lipoprotein,¹² body composition,¹³ and bone^{14,15} health is evident even in the pediatric population and supports the need for timely diagnosis and treatment.

The greater frequency of chromosome testing for girls relative to boys with growth-faltering was expected; Turner syndrome is a genetic condition that occurs in girls only and leads to a reduction in mean final height of 13 to 19 cm relative to the unaffected local female population.^{16,17} However, chromosome testing was obtained for only 1.4% of the growth-faltering girls, and 35% of these girls were at least 12

TABLE 3 Characteristics of Children With Growth-Faltering Who Received Gender-Associated Testing

	Chromosomes (n = 27)	Not Tested (n = 2980)	P	GH/IGF Axis (n = 42)	Not Tested (n = 2965)	P
Height z score, mean $\pm$ SD	-2.3 ± 0.5	-1.5 ± 1.0	<.0005	-2.4 ± 0.5	-1.5 ± 1.0	<.0001
Female, %	74	46	<.01	31	47	<.05
Age, mean $\pm$ SD, y	5.5 ± 5.4	4.9 ± 5.3	.56	6.6 ± 5.1	4.9 ± 5.3	<.05
Race, %			.61			.51
Black	89	82		79	82	—
White	7	9		14	9	—
Ethnicity, % Hispanic	4	2	.37	2	2	.67
Medicaid, %	81	74	.70	71	74	.46
No. of PCP encounters, mean $\pm$ SD	3.3 ± 2.9	1.8 ± 1.5	<.0001	3.3 ± 2.1	1.8 ± 1.5	<.0001
PCP gender, % male	11	22	.17	14	22	.23

PCP indicate primary care pediatrician.

FIGURE 2

Age distribution, according to gender, of growth-faltering children who received the gender-associated laboratory tests. A, Total number of children with chromosome testing according to year of age at the time of testing. B, Total number of children with GH/IGF axis testing according to year of age at the time of testing.

years old. These results concur with those of a review from the Turner Syndrome Clinic at the University of North Carolina. Short stature was found to be the key to diagnosis in childhood and adolescence; despite the salience of gonadal dysgenesis as a characteristic feature of this syndrome, no diagnosis was made on the basis of delayed puberty alone. Nonetheless, for the girls at the University of North Carolina Turner Syndrome Clinic, the mean delay to diagnosis after their height had fallen to below the 5th percentile was still 5.2 years.¹⁸

Even if we were to multiply 1.4% by a factor of 6 (our 3-year window of ob-

servation is one-sixth of the 18 years of pediatric care), 8.4% still falls far short of current recommendations to test chromosomes for every girl with unexplained growth failure to improve the timely diagnosis and medical care of Turner syndrome.^{18–21} Timely diagnosis is important for the initiation of proper monitoring and treatment of syndrome-associated complications such as renal and cardiac congenital malformations, neurosensory hearing loss, and neurocognitive issues.^{22,23} Ongoing surveillance for patients with Turner syndrome is needed, even for those without congenital heart disease, because of the increased inci-

dence of life-threatening aortic dissection.^{19,21,23–27} The overall standardized mortality ratio for women with Turner syndrome was calculated as 2.86 (95% confidence interval: 2.18–3.55).²⁴ Thus, preventive measures such as more aggressive management of hypertension (also an associated feature of Turner syndrome), avoidance of vigorous isometric exercise, and monitoring for aortic dilation have been recommended for women with Turner syndrome to prevent dissection.^{21,23}

Similar to GH deficiency, delayed diagnosis of Turner syndrome limits the effectiveness of GH therapy in improving adult height.²⁸ Although it is undesirable to do so, pediatric endocrinologists often compensate for late diagnoses by withholding estrogen replacement and epiphyseal closure for several years to increase the time for GH therapy to have an effect. Thus, to compound the psychosocial stress of dealing with the new diagnosis, these girls and their parents are presented with the dilemma of choosing between increased adult height and timely pubertal development. The growing appreciation for the need for age-appropriate sex hormone production for bone health²⁹ adds to the adverse consequences of a late diagnosis of Turner syndrome. Turner syndrome is a known risk for osteoporosis, and low cortical bone mineral density is apparent even before puberty in these girls.²⁷ However, when Turner syndrome is diagnosed at younger ages, GH therapy can lead to normal adult height with timely initiation of estrogen replacement.^{30,31} Thus, it is particularly concerning that 35% of the girls with growth-faltering and chromosome testing in our study were already at least 12 years old.

There are several limitations to our study. First, the frequencies of diagnostic testing and subspecialist evaluations were likely underestimates, be-

cause our population was followed longitudinally for 3 years, not their entire childhood. However, because all ages from 6 months to 20 years were represented without selection, it would be expected to produce a proportionate sampling of the entire frequencies. Second, although the majority of children in these primary care practices obtain subspecialist care within the same pediatric network, data of those who sought subspecialists at other institutions were not captured. These missed subspecialist appointments were not expected to be skewed along race or gender characteristics.

The converse limitation also holds and is important when comparing these results to those from analyses of children who were seeking short-stature evaluation in our endocrinology clinic.¹ Our endocrinology clinic received referrals from all 33 primary care practices within our pediatric network as well as nonaffiliated regional and national pediatric and family care practices. The pediatric network spans 3 states in the Delaware Valley and represents racially and socioeconomically heterogeneous populations. Because of the temporal sequence by which the primary care practices adopted the electronic health records system, 3-year longitudinal data were

available only for 4 urban, predominantly black and Medicaid-insured practices. The excess of boys seen among the predominantly white children who received short-stature evaluations in our endocrine clinic¹ was not evident among the children who were receiving endocrine care in this current study. However, a significant racial disparity was found: there was an underrepresentation of black children among those with growth-faltering who saw an endocrinologist. Thus, to further examine the interactions between race, insurance, and gender among children who received subspecialty endocrine care for growth-faltering, additional studies comparing urban to nonurban, predominantly white, privately insured primary care practices is planned as sufficient electronic longitudinal data become available.

CONCLUSIONS

A majority of children with growth-faltering are managed by primary care physicians. Girls with growth-faltering were screened for deficiencies of the GH/IGF axis only half as often as boys and did not receive chromosome testing as frequently or at the young age currently recommended for the management of Turner syndrome. Black children with growth-faltering were less likely to be referred to endocrine

subspecialists, a racial difference that was unrelated to insurance-coverage status in this cohort. By reducing the practice of overlooking poor growth in girls and black children, we can increase our diagnostic sensitivity and improve clinical outcomes for these children.

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