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Clinical Research Article

Factors Associated With Response to Growth Hormone in Pediatric Growth Disorders: Results of a 5-year Registry Analysis

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Abstract

Context: Growth hormone (GH) therapy can increase linear growth in patients with growth hormone deficiency (GHD), Turner syndrome (TS), Noonan syndrome (NS), and Prader-Willi syndrome (PWS), although outcomes vary by disease state.

Objective: To assess growth and identify factors associated with growth response with long-term GH therapy.

Methods: Data from pediatric patients with GHD, TS, NS, and PWS obtained at GH treatment initiation (baseline) and annually for 5 years in the ANSWER Program and NordiNet® IOS were analyzed retrospectively. Height standard deviation score (HSDS) was assessed over time, and multivariate analyses determined variables with significant positive effects on growth outcomes in each patient cohort.

Results: Data from patients with GHD (n = 12 683), TS (n = 1307), NS (n = 203), and PWS (n = 102) were analyzed. HSDS increased over time during GH treatment in all cohorts. Factors with significant positive effects on ΔHSDS were younger age at GH initiation and lower HSDS at baseline (all cohorts) and higher GH dose (GHD and TS only); sex had no effect in any cohort. The modeling analysis showed that ΔHSDS was greatest in year 1 and attenuated over consecutive years through year 5. Estimated least-squares mean ΔHSDS values at year 5 by cohort were 1.702 (females) and 1.586 (males) in GHD, 1.033 in TS, 1.153 in NS, and 1.392 in PWS.

Conclusion: Long-term GH therapy results in large increases in HSDS in patients with GHD, TS, NS, and PWS. Greater gains in HSDS can be obtained with higher GH doses and earlier initiation of treatment.

Key Words: human growth hormone, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, registries, multivariate analysis

Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; HSDS, height standard deviation score; IGF-I, insulin-like growth factor I; LS, least-squares; NS, Noonan syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome.

Growth hormone (GH) is essential for the promotion of linear growth in childhood. Insufficient GH activity, which is observed in a range of disease states, can lead to short stature in childhood and/or adulthood. Some of these conditions include growth hormone deficiency (GHD), typically associated with pituitary or hypothalamic dysfunction leading to reduced GH concentrations [1]; Turner syndrome (TS), which is caused by complete or partial absence of one X chromosome [2]; and Noonan syndrome (NS) and Prader-Willi syndrome (PWS), which result from autosomal genetic mutations [3, 4].

The main treatment to improve height outcome for patients with these conditions is administration of recombinant human GH therapy [1-4]. Although this is highly effective in improving linear growth toward the normal adult range, heterogeneity in disease mechanisms and patient characteristics can result in wide variations in growth outcomes. For example, different dose-response relationships have been reported in boys vs girls with GHD who are treated with GH [5], while in patients with NS, older age at GH treatment initiation is associated with reduced growth outcomes [6]. Moreover, as PWS is also the most common genetic cause of life-threatening obesity, establishing and maintaining a body mass index (BMI) value in the normal adult range is another important goal of GH therapy for these patients [4, 7].

Although extensive knowledge about various disease states and patient outcomes has been obtained through many large-scale observational studies involving patients treated with GH [8-13], efforts to optimize patient outcomes with GH therapy for specific indications remain ongoing. The ANSWER Program and the NordiNet® IOS were complementary, large-

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scale, noninterventional studies that have yielded many important findings on the long-term effectiveness and safety of treatment with Norditropin® (somatropin) in the real-world setting [14-17]. Here, we used data from the ANSWER Program and NordiNet® IOS to characterize linear growth outcomes over a 5-year period in pediatric patients with GHD, TS, NS, and PWS and to identify patient- and treatment-specific factors that significantly affect growth outcomes in these patients.

Methods

Data Source

This analysis was performed using anonymized data from the ANSWER Program (ClinicalTrials.gov identifier: NCT01009905) and NordiNet® IOS (ClinicalTrials.gov identifier: NCT00960128) collected between 2006 and 2016. Both studies have previously been described in detail [18]. Briefly, the ANSWER Program was conducted from June 2002 to September 2016 at 207 clinics in the United States, and NordiNet® IOS between April 2006 and December 2016 at 469 clinics in 22 countries in Europe and the Middle East. Both studies were approved by ethics committees and were performed in accordance with the Declaration of Helsinki, Guideline for Good Pharmacoepidemiology Practices, and local regulatory requirements. All patients provided informed, written consent.

Patients

Eligible patients were aged 0 to 18 years, diagnosed with GHD, TS, NS, or PWS, and received no GH therapy before enrolling into ANSWER or NordiNet® IOS. Patients were also required to have a height of 35 to 200 cm and a height standard deviation score (HSDS) of −5 to +2 at enrollment (baseline) and have at least one valid HSDS measurement during an annual follow-up visit. If a datapoint fell within the following ranges at any visit, all data from that visit were excluded from analyses: height <35 or >200 cm, blood insulin growth factor I (IGF-I) concentration of <1 or >1000 ng/mL, IGF-I SDS < −10 or >+10, HSDS < −5 or >+3, or GH dose <0.01 or >0.15 mg/kg/d.

Procedures and Outcomes

Analyses were performed within cohorts of patients with GHD, TS, NS, and PWS using data collected at baseline (registry enrollment, corresponding with GH treatment initiation) and once each subsequent year at annual follow-up visits through year 5 at ANSWER and NordiNet® IOS study sites. Demographic data were collected at baseline, and auxological and biochemical data and GH dose were collected by physicians at baseline and annual follow-up visits using web-based, electronic case report forms as previously described [18].

Growth responses were analyzed longitudinally within cohorts based on HSDS at baseline and each follow-up year and the change from baseline in HSDS (ΔHSDS) at each follow-up year. Multivariate analyses were performed to determine whether the year of follow-up, patient sex, HSDS at baseline, age at GH treatment initiation, GH dose during the previous year, and region (United States or Europe) significantly affected ΔHSDS within each disease cohort. For patients with PWS only, the same factors were tested to determine whether they affected change from baseline in BMI (ΔBMI) SDS.

Statistical Analyses

Patient demographics and disease characteristics at baseline were summarized using descriptive statistics as mean ± SD for continuous variables and n (%) for categorical variables. Longitudinal data for observed outcomes (as absolute values and change from baseline) at baseline and each year of follow-up were also summarized.

Factors with significant predictive value for affecting height outcomes over time were analyzed using a repeated-measures regression analysis for ΔHSDS separately for each patient cohort, with adjustments for the covariates of age at treatment start, HSDS at baseline, and average GH dose over the previous year. Longitudinal growth responses over follow-up years 1 to 5 were evaluated to provide indicator variables allowing for differences in improvement from baseline across the 5 years. The dose in the previous year was used to account for the delay between treatment administration and physiological response. This same approach was used to analyze covariates that significantly affected ΔBMI SDS in patients with PWS only.

These analyses were performed using a fixed-effects linear regression model that employed a variance-covariance model matrix incorporating correlations for all of the observations arising from the same patient, using the compound symmetry structure that assigned equal intrapatient correlations. The data were assumed to be Gaussian, and their likelihood was maximized to estimate the model parameters. All patient annual records were used, irrespective of loss to follow-up or potential gaps in annual records, with no imputation for missing values. The contribution of interactions of covariates with indicators for each follow-up year over and above the main effects were tested. Model coefficient estimates and least-squares (LS) means based on the model-predicted outcomes for an average patient (± SE or 95% CI) were reported. *P* values were derived, and significance was defined as $P < .05$ with no adjustment for multiple testing. All analyses were performed using SAS, version 9.4.

Results

Patients

A total of 14 295 patients were included in the analyses: 12 683 were diagnosed with GHD (88.7%), 1307 with TS (9.1%), 203 with NS (1.4%), and 102 with PWS (0.7%). Patients were similarly distributed between the ANSWER Program (51.2%) and NordiNet® IOS (48.8%); however, a slightly larger proportion of patients with NS originated from ANSWER (60.0%), and TS from NordiNet® IOS (64.2%).

Most patients with GHD and NS were male (70.3% and 72.9%, respectively), the PWS cohort was well balanced by sex (51.0% females; 49.0% males), and all patients with TS were female (100%), as consistent with the mutational profile of the disease (Table 1). The youngest patient cohort was PWS, which had a mean age at GH initiation of 4.99 ± 5.01 years, considerably lower than in the other cohorts. The mean starting dose of GH in each cohort was consistent with prescribing recommendations for the respective indications (Table 1).

Table 1. Baseline demographics and disease characteristics

	GHD		NS	PWS	TS
Sex	n = 12 683		n = 203	n = 102	n = 1307
Male, n (%)	8917 (70.3)		148 (72.9)	50 (49.0)	0 (0)
Female, n (%)	3766 (29.7)		55 (27.1)	52 (51.0)	1307 (100)
Age at GH start, years	**Female (n = 3766)** 9.08 ± 3.76	**Male (n = 8917)** 10.37 ± 3.98	n = 203 9.04 ± 3.80	n = 102 4.99 ± 5.01	n = 1307 8.63 ± 3.85
Bone age/chronological age	n = 1799 0.83 ± 0.22	n = 4205 0.84 ± 0.19	n = 91 0.85 ± 0.22	n = 23 0.90 ± 0.26	n = 657 0.88 ± 0.20
Height SDS	n = 3766 −2.47 ± 1.14	n = 8917 −2.21 ± 1.01	n = 203 −2.66 ± 1.02	n = 102 −1.57 ± 1.52	n = 1307 −2.62 ± 0.94
Height, cm	n = 3766 118.05 ± 22.46	n = 8917 126.48 ± 22.99	n = 203 116.68 ± 20.26	n = 102 95.15 ± 33.01	n = 1307 114.80 ± 19.75
Weight SDS	n = 2699 −1.55 ± 1.51	n = 6807 −1.38 ± 1.42	n = 169 −2.06 ± 1.12	n = 83 −0.53 ± 2.11	n = 912 −1.17 ± 1.28
BMI SDS	n = 3702 −0.16 ± 1.29	n = 8806 −0.15 ± 1.32	n = 200 −0.44 ± 1.14	n = 79 0.88 ± 1.78	n = 1280 0.41 ± 1.08
IGF-I SDS	n = 2254 −1.66 ± 1.57	n = 5322 −1.63 ± 1.70	n = 85 −1.29 ± 1.65	n = 52 −0.88 ± 1.82	n = 695 −0.83 ± 1.53
GH dose, mg/kg/d	n = 3766 0.037 ± 0.012	n = 8917 0.038 ± 0.012	n = 203 0.042 ± 0.012	n = 102 0.031 ± 0.013	n = 1307 0.045 ± 0.011
Height velocity SDS	n = 418 −0.79 ± 1.76	n = 867 −0.75 ± 1.72	n = 21 −0.36 ± 1.31	n = 8 −0.63 ± 1.11	n = 132 −1.00 ± 1.77

Values are mean ± SD unless otherwise noted.
Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IGF-I, insulin-like growth factor I; NS, Noonan syndrome; PWS, Prader-Willi syndrome; SDS, standard deviation score; TS, Turner syndrome.

GH dosing at baseline and each follow-up year is summarized by disease cohort and registry in Fig. 1. The mean baseline dose of 0.037 mg/kg/d in the GHD cohort was comparable to the maximum indicated dose of 0.034 mg/kg/d for that indication; however, dosing at baseline and over the analysis period was markedly lower in patients in NordiNet® IOS than in the ANSWER Program, likely reflecting the higher approved dose ranges for other rhGH products in the United States [19-21]. The mean GH dose at initiation in the TS and NS cohorts was 0.045 mg/kg/d and 0.042 mg/kg/d, respectively, and remained essentially unchanged over time in the TS cohort, while dosing for patients with NS increased slightly from baseline to year 3 before returning to near baseline concentrations by year 5 (Fig. 1).

Longitudinal Analyses

Results of the longitudinal analysis of growth over the first 5 years of GH therapy showed that patients in all disease cohorts experienced increases in HSDS over time (Table 2). All cohorts showed increases in HSDS over the first 3 years, with the largest increase occurring during the first year, with sequentially attenuated increases over the ensuing 2 years (Table 2). Patients with GHD showed the most consistent increases over the entire analysis period, while patients with TS also showed HSDS increases each consecutive year, although the increases were small after year 2. Patients with NS and PWS showed increases in HSDS that peaked at year 3, after which patients with NS showed an additional increase of only 0.05 by year 5. The ΔHSDS data (Table 3) further support the long-term improvements in HSDS after initiation of GH treatment.

Factors Associated With Increases in HSDS

The repeated-measures analyses revealed several factors that significantly affected the HSDS response to treatment with GH (Table 4). First, patient age at GH treatment initiation had a significant effect across all indications. Specifically, for each year that initiation of GH therapy was delayed, the increase in HSDS was reduced by estimated values of 0.05 (females) and 0.04 (males) in GHD, 0.02 in TS, 0.03 in NS, and 0.08 in PWS. Second, a higher HSDS at baseline resulted in a smaller increase in HSDS over time. Specifically, each 1-unit increase in baseline HSDS corresponded to HSDS improvements over time that were reduced by approximately 0.2 in GHD, 0.16 in TS, 0.08 in NS, and 0.40 in PWS. Third, a higher dose of GH in the previous year was associated with greater increases in HSDS among patients with GHD and TS. Specifically, an increase of 0.01 mg/kg/d GH was estimated to increase HSDS by a value of 0.03 (females) and 0.02 (males) in GHD and 0.03 in TS. Although statistical significance was not achieved in NS and PWS, trends were positive, suggesting increased HSDS outcomes with increasing GH doses. Sex was not identified as a significant factor for HSDS in any cohort (excluding TS, who were all female). Regarding region, significant increases in HSDS were found in males with GHD ($P < .0001$) in the US-based ANSWER Program, and with TS ($P = .0306$) in the European-based NordiNet® IOS Program (not shown).

An assessment of cumulative HSDS changes over time revealed that HSDS improvements were significantly increased at each subsequent year compared with year 1; however, the HSDS response attenuated over time, particularly from year 4 to year 5. The largest overall increases over time occurred in the GHD cohort, while the smallest increases occurred in the PWS and TS cohorts (Table 4). LS mean estimates for ΔHSDS derived from the models (representing the expected outcome for the average patient within cohorts) are plotted in Fig. 2. The results reveal the attenuated ΔHSDS responses over time for all cohorts. These plots also show that there were minimal differences between female and male patients

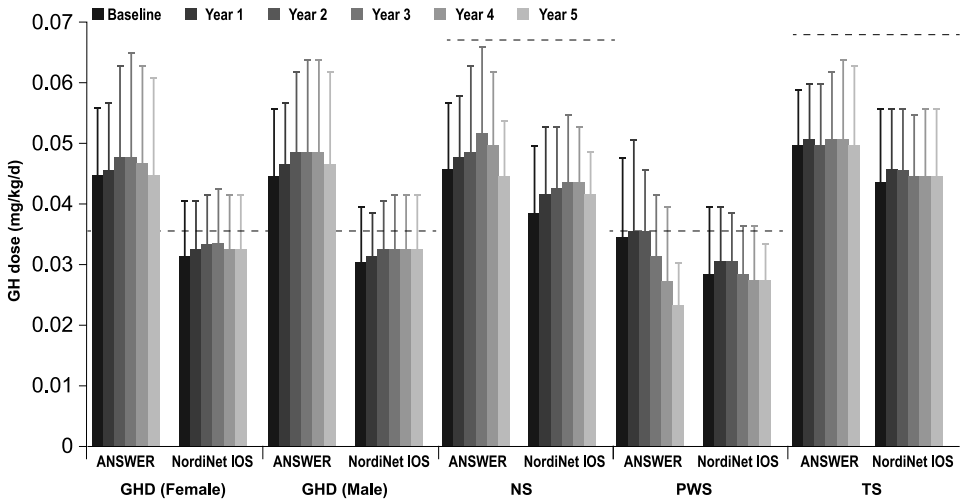

Figure 1. Mean (SD) GH dose at baseline and each follow-up year by disease cohort and registry. Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; NS, Noonan syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome. Dotted lines show indicated dosing levels based on US prescribing information.

in the GHD cohort (Fig. 2A), while patients in the other cohorts experienced smaller increases in ΔHSDS over time, with the TS cohort showing the smallest overall improvement (Fig. 2B).

The data were further analyzed to quantify the degree of variability in response to GH between different patients within cohorts. The results showed that the correlation within patients was high across all indications (range, 0.71-0.76). However, the indication with the most variable response was PWS, which had a variance of random effect between patients for ΔHSDS of 0.511, more than twice as large as the values for the NS and TS cohorts, which showed much more consistent responses to GH (variance of 0.203 and 0.216, respectively) (Table 4).

Factors Associated With Increases in BMI SDS Among Patients With PWS

In the analysis of ΔBMI SDS in the PWS cohort, large increases in BMI SDS occurred at years 3, 4, and 5 compared with the increase at year 1, although there was no additional gain at year 5 compared with year 4. The BMI SDS value at baseline had a significant effect on the outcome, as every 1-point increase in baseline BMI SDS corresponded to a 0.5-point decrease in follow-up ΔBMI SDS (Table 5).

Discussion

This analysis of patients from the ANSWER Program and the NordiNet® IOS confirmed that administration of GH therapy increases linear growth in pediatric patients with one of several indications associated with insufficient GH activity. The study results suggest significant increases in ΔHSDS over 5 years of treatment with GH, with the strongest effects on growth observed among patients with GHD. Increases were similar between male and female patients with GHD, unlike previous findings that suggested females have a reduced growth response to GH compared with males [5, 22]. The smallest increases in linear growth were observed for patients with TS. We also observed that younger patient age at GH initiation, lower HSDS at baseline, and higher average daily dose of GH significantly predict improved linear growth outcomes in pediatric patients with GHD, TS, NS, and PWS.

Our longitudinal analysis revealed that patients in all cohorts experienced periods of catch-up growth after initiation of GH therapy, which is characterized by a brief period of growth that exceeds the normal rate for age and sex after GH initiation and is essential for approximating normal adult height [23, 24]. Although this is common across indications that require GH therapy, the characteristics of this phase vary by disease state, individual patient factors, and treatment course. For example, in GHD, catch-up growth can occur over 7 years or more but is most apparent within the first 3 years of GH therapy and can be affected by the onset of puberty [25-29]. Catch-up growth has also been associated with positive outcomes in TS [30, 31] and PWS [32]. Although patients with NS also experience catch-up growth, the extent is significantly influenced by the mutational profile of the patient [33].

Our findings also identified important patient- and treatment-related predictors of linear growth outcomes with GH therapy. First, the mean dose of GH in the previous year was positively correlated with subsequent growth outcomes in all patient cohorts. Although not formally analyzed, the TS and NS cohorts, which showed the smallest increases in linear growth, were the cohorts with the largest differences between the average doses administered and the maximum doses indicated in the label. Specifically, the mean initial GH dose in TS was 0.045 mg/kg/d compared with a maximum indicated dose of 0.067 mg/kg/d, while in NS, the mean initial dose was 0.042 mg/kg/d compared with a maximum indicated dose of 0.066 mg/kg/d [7, 19]. The mean initial dose in the GHD cohort, which showed the greatest increases overall, was 0.037 mg/kg/d, which was more closely aligned with its maximum indicated dose of 0.034 mg/kg/d. In this real-world study, we were not able to determine the reasons for increasing or decreasing the dose beyond the weight basis.

Younger age at GH treatment initiation was also significantly associated with improved linear growth outcomes, which has been shown previously [26, 34, 35]. This is not surprising considering that most linear growth occurs before puberty, which can affect the potential for catch-up growth [24, 29, 31, 36]. These results are consistent with previous

Table 2. Longitudinal summary statistics for height SDS

Assessment	GHD		NS	PWS	TS
	Female	Male			
Baseline	n = 3766 −2.47 ± 1.14	n = 8917 −2.21 ± 1.01	n = 203 −2.66 ± 1.02	n = 102 −1.57 ± 1.52	n = 1307 −2.62 ± 0.94
Year 1	n = 3343 −1.76 ± 1.09	n = 7949 −1.55 ± 0.98	n = 177 −2.14 ± 1.07	n = 90 −0.81 ± 1.37	n = 1142 −2.09 ± 0.95
Year 2	n = 2604 −1.39 ± 1.11	n = 6110 −1.2 ± 1.01	n = 129 −1.9 ± 1.14	n = 69 −0.51 ± 1.29	n = 965 −1.8 ± 0.96
Year 3	n = 1859 −1.19 ± 1.11	n = 4517 −0.99 ± 1.02	n = 96 −1.61 ± 1.21	n = 59 −0.28 ± 1.06	n = 772 −1.68 ± 0.94
Year 4	n = 1289 −1.04 ± 1.15	n = 3088 −0.88 ± 1.03	n = 75 −1.67 ± 0.98	n = 49 −0.35 ± 1.13	n = 597 −1.65 ± 0.94
Year 5	n = 856 −0.97 ± 1.2	n = 2017 −0.81 ± 1.07	n = 56 −1.56 ± 0.97	n = 33 −0.39 ± 1.18	n = 460 −1.58 ± 0.88

Values are mean ± SD.
Abbreviations: GHD, growth hormone deficiency; NS, Noonan syndrome; PWS, Prader-Willi syndrome; SDS, standard deviation score; TS, Turner syndrome.

Table 3. Longitudinal summary statistics for ΔHSDS

Assessment	GHD		NS	PWS	TS
	Female	Male			
Year 1	n = 3343 0.70 ± 0.57	n = 7949 0.64 ± 0.52	n = 177 0.47 ± 0.39	n = 90 0.79 ± 0.94	n = 1142 0.54 ± 0.40
Year 2	n = 2604 1.12 ± 0.76	n = 6110 1.04 ± 0.69	n = 129 0.83 ± 0.58	n = 69 1.06 ± 1.09	n = 965 0.81 ± 0.55
Year 3	n = 1859 1.40 ± 0.87	n = 4517 1.32 ± 0.81	n = 96 1.02 ± 0.61	n = 59 1.24 ± 1.20	n = 772 0.96 ± 0.64
Year 4	n = 1289 1.63 ± 0.98	n = 3088 1.50 ± 0.88	n = 75 1.03 ± 0.62	n = 49 1.29 ± 1.30	n = 597 1.00 ± 0.70
Year 5	n = 856 1.81 ± 1.08	n = 2017 1.65 ± 0.96	n = 56 1.17 ± 0.69	n = 33 1.60 ± 1.28	n = 460 1.05 ± 0.71

Values are mean ± SD.
Abbreviations: ΔHSDS, change from baseline in height standard deviation score; GHD, growth hormone deficiency; NS, Noonan syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome.

studies demonstrating that growth outcomes can be largely restored when GH is initiated early [31, 36-43].

Interestingly, we found that treatment in European countries was associated with greater improvements in growth outcomes in patients with TS, whereas treatment in the United States was associated with greater ΔHSDS for males with GHD. As patients with TS in both regions received comparable doses of GH, other aspects of treatment must have contributed to this effect. These could have included differences in treatment access and continuity of care, differences in diagnostic testing approaches or availability, or local guidelines regarding administration of oxandrolone or estrogen, which are coadministered with GH to enhance growth outcomes. Dosing data from the GHD cohort, however, suggest that patients in the United States (ANSWER Program) received higher doses than those in NordiNet® IOS, which may have influenced the regional effect (Fig. 1).

Because PWS is also characterized by hyperphagia and feeding behaviors that increase the risk of obesity-related complications, mortality, and reduced quality of life [4, 7, 32], we also investigated predictors of ΔBMI SDS; this revealed that only duration of treatment and lower baseline BMI SDS were significantly associated with improved ΔBMI SDS outcomes. Despite previous findings suggesting that increased GH exposure can predict increases in both linear growth and body fat percentage [32], we did not find any association between BMI SDS and GH dose, nor any effects of region, sex, or age at treatment initiation. However, performing such analyses on this population is particularly challenging considering the rarity of disease, which leads to small study samples with high variability across parameters. Moreover, the results of the variability analysis suggest that PWS is the indication with the highest degree of uncertainty that a good a response to GH therapy will be achieved, while NS and TS had the lowest variability, suggesting more consistent responses are likely. This may result from heterogeneity among patients with PWS, who exhibit ranges of GH deficiency, linear growth patterns, and BMI/obesity, potentially affecting outcomes from GH therapy. By contrast, the more specific genetic profile of TS leads to a patient population with more homogeneous clinical characteristics.

In total, these results are encouraging, as they suggest that growth outcomes for patients with deficient GH activity across multiple indications can be improved by modifying

Table 4. Summary of repeated-measures model effect sizes (effect coefficients ± SE)

	GHD		NS	PWS	TS
	Female	Male			
Age at GH start, years	−0.047 ± 0.003‡	−0.041 ± 0.002‡	−0.033 ± 0.009†	−0.077 ± 0.016‡	−0.020 ± 0.004‡
Baseline HSDS	−0.206 ± 0.010‡	−0.204 ± 0.007‡	−0.077 ± 0.034*	−0.401 ± 0.053‡	−0.161 ± 0.015‡
GH dose from previous year, mg/kg/d	3.315 ± 0.632‡	2.354 ± 0.372‡	1.749 ± 1.882	6.574 ± 4.531	3.496 ± 0.773‡
Years of follow-up					
2	0.396 ± 0.009‡	0.387 ± 0.006‡	0.324 ± 0.034‡	0.249 ± 0.076*	0.258 ± 0.014‡
3	0.656 ± 0.011‡	0.653 ± 0.007‡	0.518 ± 0.038‡	0.391 ± 0.082‡	0.406 ± 0.015‡
4	0.841 ± 0.012‡	0.817 ± 0.008‡	0.626 ± 0.042‡	0.454 ± 0.087‡	0.464 ± 0.016‡
5	0.969 ± 0.015‡	0.921 ± 0.009‡	0.689 ± 0.045‡	0.563 ± 0.102‡	0.505 ± 0.018‡
Variability					
ΔHSDS variation within patient	0.112	0.101	0.07	0.198	0.087
ΔHSDS variation between patient	0.358	0.300	0.203	0.511	0.216
Intrapatient correlation	0.761	0.748	0.743	0.721	0.712

Region (United States or Europe) was also included as an indicator variable in the models and had a significant effect for GHD males ($P < .0001$) and TS ($P < .05$). Sex was included in the models for NS and PWS and did not have a significant effect in either model. *$P < .05$; †$P < .001$; ‡$P < .0001$
Abbreviations: ΔHSDS, change in height standard deviation score; GH, growth hormone; GHD, growth hormone deficiency; NS, Noonan syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome.

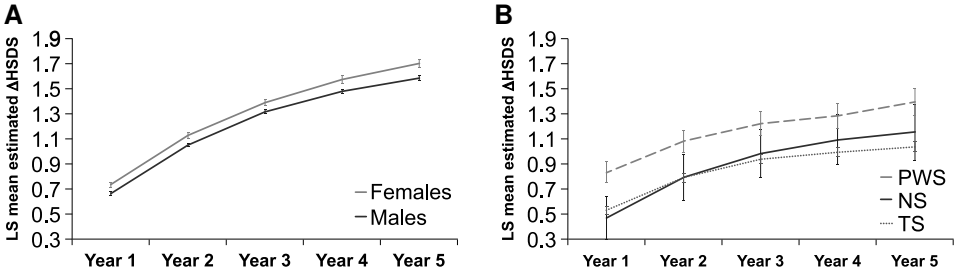

Figure 2. Model-based mean estimates for ΔHSDS over time in patients with (A) GHD, and (B) PWS, NS, and TS. Abbreviations: GHD, growth hormone deficiency; ΔHSDS, change in height standard deviation score from baseline; LS, least-squares; NS, Noonan syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome. Error bars indicate 95% CI.

treatment approaches. For example, steps taken to establish earlier diagnosis that could result in earlier GH treatment initiation would allow for GH treatment during a larger proportion of the critical period when catch-up growth is most likely to occur. These results also suggest that greater emphasis on administering GH at doses closer to the upper end of the indicated dose range may further ensure that patients are achieving optimal benefits from GH administration.

This study was unique for its large, longitudinal, multicenter design that included real-world data across demographically and geographically diverse patients with multiple diagnoses. The data available from these registries also allow for longer follow-up than may be possible in a clinical-trial setting. Additionally, although our findings are similar to those from prior registry studies [44-46], by supporting those findings with growth data from some of the largest real-world cohorts to date for these disorders, and the longest observation period for studies of this kind (5 years), which could provide clinicians with additional assurance and perhaps a more reliable indication of the size of the impact on growth one can expect when prescribing growth hormone in clinical practice. Although studies that comprise dozens or even hundreds of patients have shown similar associations between covariates, the robust statistical analysis and large sample sizes reported here can provide tangible estimates that can be applied to patients from similar populations and be effectively used to assist with shared decision making and patient counseling.

Limitations of observational data that apply here include potential positive biases with respect to loss to follow-up, which may have occurred because of GH treatment discontinuation or switch to a brand of GH other than Norditropin®, and that would necessitate discontinuation from the ANSWER Program or NordiNet® IOS. Furthermore, due to a lack of data for variables such as IGF-I concentrations, dosing adherence, and height velocity, we were unable to include these in the present regression analyses. The results may have also been affected by changes in GH dosage that could have occurred as a result of insufficient response, although we attempted to mitigate the effect of this possibility by using the dose over the previous year as the potential factor affecting the outcome during the current year. The study was also limited by the overall relatively low prevalence of NS and PWS, which limited the sample sizes for those cohorts, and which were reduced further over time because of patient attrition.

In conclusion, the results of this retrospective analysis of data from the ANSWER Program and NordiNet® IOS that included 5 years of GH therapy suggest that long-term

Table 5. Summary of repeated-measures model effect sizes for ΔBMI SDS in all patients with PWS

Variable	Coefficient estimate ± SE
Age at GH start, years	0.028 ± 0.029
Baseline BMI SDS	−0.511 ± 0.080‡
GH dose from previous year, mg/kg/d	7.282 ± 8.772
Years of follow-up	
2	0.161 ± 0.133
3	0.360 ± 0.145*
4	0.486 ± 0.155*
5	0.494 ± 0.184*

Region (United States or Europe) and sex were also included in the model and did not have a significant effect. *$P < .05$; ‡$P < .0001$.
Abbreviations: ΔBMI SDS, change in body mass index standard deviation score; GH, growth hormone; PWS, Prader-Willi syndrome.

administration of GH results in significant positive effects on growth in patients with GHD, TS, NS, and PWS. The largest increases in HSDS occurred in patients with GHD, while those with TS showed the smallest growth response. Male and female patients showed similar increases in all cohorts (excluding TS, which does not affect males). Based on these results, further improvements in patient outcomes may be possible by optimizing GH dosing and initiating therapy earlier in the disease course. Further investigations into long-acting GH preparations may also impact future growth outcomes.

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Data Availability

Some data sets generated during and/or analyzed during the current study may be available from the corresponding author on reasonable request.

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