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Long-Term Response to GH Therapy in Short Children With a Delayed Infancy-Childhood Transition (DICT)

KERSTIN ALBERTSSON-WIKLAND, BERIT KRISTRÖM, BJÖRN JONSSON, AND ZE'EV HOCHBERG

Göteborg Pediatric Growth Research Center (GP-GRC), [K.A.-W., B.K.], The Sahlgrenska Academy at University of Gothenburg, SE-41685 Gothenburg, Sweden; Department of Clinical Science [B.K.], Umeå University, SE-90185 Umeå, Sweden; Department of Women and Child Health [B.J.], Uppsala University, SE-75185 Uppsala, Sweden; Department of Pediatric Endocrinology [Z.H.], Meyer Children's Hospital at Rambam Medical Center, 31096 Haifa, Israel

ABSTRACT: Transition of growth from infancy to childhood is associated with activation of the GH-IGF-I axis. Children with a delayed infancy-childhood transition (DICT) are short as adults. Thus, age at ICT may impact on growth response to GH. The objective was to investigate associations between growth response to GH treatment and ICT timing in children with idiopathic short stature (ISS) in a randomized, controlled, multicenter trial, TRN 88-080. A total of 147 prepubertal children (mean age, 11.5 ± 1.4 y) were randomized to receive GH 33 μg/kg/d (GH_{33}, $n = 43$), GH 67 μg/kg/d (GH_{67}, $n = 61$), or no treatment ($n = 43$). Data on growth to final height (FH) were analyzed after categorization into those with normal ($n = 76$) or delayed ICT ($n = 71$). Within the GH_{33} group, significant height gain at FH was only observed in children with a DICT ($p < 0.001$), with each month of delay corresponding to gain of 0.13 SD score (SDS). For the GH_{67} group, the timing of the onset of the ICT had no impact on growth response. In conclusion, ISS children with a DICT responded to standard GH dose (better responsiveness), whereas those with a normal ICT required higher doses to attain a significant height gain to FH. **(*Pediatr Res* 69: 504–510, 2011)**

The term idiopathic short stature (ISS) is used to describe stature in children who are short compared with their peers for unknown reasons. This definition is assigned after the exclusion of systemic diseases, hormone deficiencies, psychosocial deprivation, genetic diseases, and syndromes known to cause short stature (1). Among children classified as having ISS, there is great variability in factors such as height, BMI, IGF-I, IGF-binding protein 3 (IGFBP3) levels, degree of bone maturation, and timing of puberty. The considerable variability that is seen suggests that diverse underlying mechanisms are responsible for the observed growth impairment.

We have recently defined a second and larger subgroup of short individuals who have experienced a delay in the onset of the infancy-childhood transition (ICT) so-called DICT (2,3). As many as 50% of cases of ISS can be explained by a delay in ICT, and such children show evidence of dysfunction within the GH-IGF-I hormone axis (2).

Recombinant human GH has been used to treat short stature in children with GH deficiency (GHD) since 1986 (4). This treatment has also been shown to increase growth and final height (FH) in children with ISS (5–8) and was approved for this indication by the US Food and Drug Administration in 2003. As expected for this heterogeneous population, long-term height gains vary, ranging from no gain to approximately +3 SD score (SDS) (8). Concerns about the ethical and economic ramifications of expanding the use of GH to children in whom the GH secretion is not deficient require that we have a better understanding of different mechanisms responsible for ISS and can define subgroups of patients according to their responsiveness to GH therapy. This has prompted us to explore the variables that are related to growth responsiveness to GH therapy in prediction models in children diagnosed with GHD or ISS (9–12): GH responsiveness was best estimated when incorporating information on growth during early life together with the GH maximum (GH_{max}) spontaneous secretion (12) and useful for guiding GH dosing in a randomized clinical trial (13). Thus, the most important auxological factor for predicting growth in response to GH is the growth pattern during the first year of life—the greater the loss in relative height during infancy, the better will be the later growth response on GH. We now suggest this growth pattern to be a sign of the onset of activation of the GH-IGF-I effect on growth, *i.e.* the time of the ICT (2).

It has previously been shown that the GH axis becomes active during the ICT (14) and that the surge in IGF-I and IGFBP3 levels that is known to occur during the first year of life coincides with the ICT (15). The ICT has also been found to be delayed in children with GHD (2,14). These findings

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Correspondence: Kerstin Albertsson-Wikland, M.D., Ph.D., Göteborg Pediatric Growth Research Center (GP-GRC), The Sahlgrenska Academy at University of Gothenburg, SE-416 85 Göteborg, Sweden; e-mail: kerstin.albertsson-wikland@pediat.gu.se

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Abbreviations: AGA, appropriate for GA; **AITT,** arginine-insulin tolerance test; **DICT,** delayed infancy-childhood transition; **diffMPH$_{SDS}$,** difference in child height$_{SDS}$ *versus* midparental height (MPH)$_{SDS}$; **FH,** final height; **GH$_{33}$,** GH dose 33 μg/kg/d; **GH$_{67}$,** GH dose 67 μg/kg/d; **GHD,** growth hormone deficiency; **GH$_{max}$,** maximum peak of GH; **ICP,** infancy-childhood-puberty; **ICT,** infancy-childhood-transition; **ISS,** idiopathic short stature; **IGFBP3,** insulin-like growth-factor-I-binding protein 3; **ITT,** intention-to-treat; **MPH,** midparental height; **non-DICT,** normal infancy-childhood-transition; **PP,** per-protocol; **SDS,** standard deviation score; **SGA,** small for GA

have led to the current working hypothesis that age at onset of ICT may be an important variable/indicator for responsiveness to GH therapy. We would predict that children with a delay in the ICT will be more sensitive to GH treatment.

The present long-term, randomized, controlled, clinical trial was undertaken to evaluate the effects of GH treatment in short children who were non-GH deficient (8). Here, we reanalyze these data to evaluate the impact of GH treatment on FH in short non-GH-deficient children who were recategorized according to whether they had a normal or delayed ICT or not. This was not an inclusion or a randomization criterion of the original study, but it was possible to evaluate this parameter because growth of all the study children during infancy was followed prospectively in Swedish well-baby clinics.

SUBJECTS AND METHODS

The randomized, controlled study was conducted in accordance with declaration of Helsinki and Good Clinical Practice in 177 short non-GH-deficient children from six pediatric endocrinology units in Sweden who were enrolled in the study between 1988 and 1999. The protocol was approved by the Ethical Committees at Universities of Göteborg, Lund, Linköping, Uppsala, and Umeå and at Karolinska Institute in Sweden. Informed consent was obtained from all children and their parents.

Of the total population of 177 children, we were unable to determine the timing of ICT in four cases due to missing measurements. A further 26 children were excluded because of protocol violation (in 14 cases GH treatment was stopped prematurely; in 12 controls, GH or testosterone treatment was given). A total of 147 children comprised the intention-to-treat (ITT) population. Subjects were randomized into three groups. Children received GH treatment either at 33 μg/kg/d (GH_{33}, $n = 43$) or 67 μg/kg/d (GH_{67}, $n = 61$), or remained untreated ($n = 43$), and ICT was found to be delayed in 49%, 53%, and 42% of the children, respectively. Age at the start of the study for girls was 11.1 ± 1.30 (range, 8–13 y) and for boys 11.7 ± 1.39 (range, 10–15 y). No subject was GH deficient, and all subjects had a height during the prestudy period below −2 SDS according to Swedish growth standards (16). Furthermore, bone age according to Tanner-Whitehouse (TW2) was ≤11 y in girls and ≤13 y in boys. None of the children had a syndrome or any chronic disease. Of the children studied, 106 were prepubertal at the start of the study and adhered completely to the protocol, defined as the per-protocol (PP) population. During the pretreatment year, 31 children entered puberty, whereas 68 remained prepubertal during the first year of treatment. Forty children were born small for GA (SGA) (17,18). In the past decade, short SGA children have been separated from the group of children with ISS (19). As the study was initiated long before this new classification, children with SGA were also included due to the randomization procedure.

Growth history. Height and weight measurements were made at neonatal, child, and school healthcare units from birth until prestudy start. An average of 9.0 ± 3.6 length/height measurements was obtained from each child before 3 y of age. Supine length measurements were taken until 2 y of age; thereafter, standing height was recorded. During the pretreatment year until FH, measurements were made using a Harpenden stadiometer at growth clinics of the university hospitals.

ICT. The data collected in the first 4 y of life of the subject were fitted using a mathematical model that incorporated the functions and concepts of the first two components of Karlberg's infancy-childhood-puberty (ICP) growth model (20), as previously described (2,14,20–22). The infancy component is modeled with a negative exponential function:

$$Y = a_1 + b_1[1 - \exp(-c_1 t)]$$

where the birth length is a_1, the postnatal contribution of the infancy component is b_1, and the growth rate of the infancy component is c_1. The childhood component is represented by a second-degree polynomial function, where t is age in years from birth:

$$Y = a_C + b_C t + c_C t^2$$

Subjects were divided into two groups based on the timing of ICT: those for whom the start of ICT was within the normal range (ICT start 6–12 mo of age, non-DICT) and those for whom the start of ICT was delayed (ICT start >12 mo of age, DICT).

All measurements were plotted on the ICP growth model growth chart (20). The timing of ICT was determined to the nearest month by two observers, with a coefficient of variation (CV) of less than 1 mo ($n = 100$), as previously described (2,14,20–22).

Growth outcome variables. Three variables were used to evaluate treatment outcome: a) FH_{SDS} (16); b) gain in $height_{SDS}$ from the start of the treatment *versus* the childhood component (20) to FH; and c) difference between FH_{SDS} and midparental $height_{SDS}$ ($diffMPH_{SDS}$). MPH_{SDS} was calculated as (father's $height_{SDS}$ + mother's $height_{SDS}$)/1.61 (23). The height, weight, and BMI (24) of the children and the height of the parents were assessed relative to Swedish population-based growth references (16). The childhood component of the ICP model was used for all measurements before puberty (20); thereafter, the ordinary combined function of childhood and puberty was used (16).

FH was defined as the height achieved when annual growth was less than 1 cm. The last height measured was used for calculations of the outcome variables *versus* the Swedish growth reference data for 18 y olds (16). Birth weight and length for GA and gender were calculated in SDS (17,18). Children were classified as being born SGA if birth length and/or weight was less than −2 SDS below the mean for GA (17,18).

Hormonal evaluation. The hormonal analyses of GH (25,26), IGF-I (27), IGFBP3 (28), and leptin (29) were performed at the GP-GRC laboratory (SWEDAC accreditation no. 1899). Arginine-insulin tolerance tests (AITT) were performed in all but two children and GH_{max} identified. Twenty-four-hour GH profiles were obtained in all subjects, with 20-min integrated or discrete samples and GH_{max} identified (25).

Statistical analyses. Statistical analyses were performed by a statistician (B.J.) using standard statistical package SPSS, version 15.0 (SPSS inc. Chicago, IL). Results are expressed as mean ± SD unless otherwise indicated. Tests for statistical significance were performed using nonparametric tests of Wilcoxon type; Wilcoxon tests for within-group changes, Mann-Whitney U tests for between-group differences, and Kruskal-Wallis tests for differences between more than two groups. t tests were applied when data were normally distributed according to a Kolmogorov-Smirnov test ($p > 0.20$): these cases will be denoted in text and tables. Simple linear regression analyses were used when correlating ICT to FH. Spearman rank correlation was applied in correlation analyses. Significance level was set at $p < 0.05$. No corrections for multiplicity have been made as the study is explorative.

RESULTS

Pretreatment characteristics. Pretreatment characteristics of the ITT and PP populations were similar. However, when subdivided into those with a normal and a delayed ICT, there were differences in characteristics at birth (Table 1). Children with DICT were born later in terms of GA and were longer and heavier at birth than non-DICT children. The ICT occurred about 4 mo later ($p < 0.001$) in the DICT group, and this delay corresponded to a significantly reduced growth rate during the first 2 y of life ($p < 0.001$).

At the start of the study, children with DICT had lower $IGF\text{-}I_{SDS}$ than non-DICT children (PP: −0.97 ± 1.19 *versus* −0.62 ± 1.02, respectively, $p < 0.05$; ITT: −0.99 ± 1.13 *versus* −0.56 ± 0.98, respectively, $p < 0.005$). GH_{max} at 24 h were similar in both groups (NS). Those with DICT were leaner (PP, $p < 0.048$; ITT, $p < 0.050$; t test) and had a greater delay of bone age (PP, $p < 0.029$; ITT, $p < 0.008$) than those with a normal ICT (Table 1). The short children born SGA did not differ in terms of pretreatment characteristics at the start of the study from ISS children born appropriate for GA (AGA).

First-year treatment response. First-year growth response was analyzed in the 68 children in the ITT population who remained prepubertal. For those receiving the GH_{33} dose, a growth response of 0.60 ± 0.19 SDS was found in the DICT group compared with 0.44 ± 0.17 SDS in the non-DICT group ($p = 0.03$). For the GH_{67} dose, the corresponding results were 0.74 ± 0.19 SDS and 0.77 ± 0.24 SDS (NS), respectively. A dose-response relationship with first-year

Table 1. *Pretreatment characteristics of the PP and ITT populations*

		PP (N = 106)				ITT (N = 147)			
	Group	N	Mean	SD	$p <$	N	Mean	SD	$p <$
At birth/early growth									
ICT, mo	Non-DICT	52	10.2	1.76		76	9.9	1.80	
	DICT	54	14.0	1.08	0.001	71	14	1.29	0.001
Δlength birth to 2 y, SDS	Non-DICT	47	−0.8	0.96		67	−0.7	1.02	
	DICT	53	−1.5	0.90	0.001	69	−1.4	0.90	0.001
GA, wk	Non-DICT	52	39.0	1.98		76	39.0	1.96	
	DICT	54	40.0	1.16	0.004	71	40.0	1.24	0.001
Birth length SDS	Non-DICT	52	−1.5	0.94		76	−1.7	1.08	
	DICT	54	−0.7	0.89	0.001	71	−0.8	0.92	0.001
Birth weight SDS	Non-DICT	52	−1.0	0.96		76	−1.2	1.05	
	DICT	54	−0.4	0.87	0.001	71	−0.5	0.92	0.001
Midparental height SDS	Non-DICT	52	−1.8	0.94		76	−1.8	0.87	
	DICT	54	−1.7	0.86	NS	71	−1.7	0.83	NS
Mother's height SDS	Non-DICT	52	−1.6	1.04		76	−1.6	0.94	
	DICT	54	−1.3	0.95	NS	71	−1.4	0.94	0.042
Father's height SDS	Non-DICT	52	−1.2	0.94		76	−1.2	0.95	
	DICT	54	−1.4	0.93	NS	71	−1.3	0.92	NS
At study start									
Pretreatment year Δheight SDS	Non-DICT	52	0.02	0.211		76	−0.11	0.380	
	DICT	54	−0.04	0.290	NS	71	−0.07	0.319	NS
Age, y	Non-DICT	52	11.14	1.248		76	11.53	1.391	
	DICT	54	11.46	1.458	NS	71	11.62	1.400	NS
Height SDS	Non-DICT	52	−2.64	0.398		76	−2.77	0.536	
	DICT	53	−2.75	0.577	NS	70	−2.78	0.590	NS
BMI SDS	Non-DICT	52	−0.69	0.871		76	−0.69	0.947	
	DICT	53	−1.08	1.105	0.048*	70	−1.02	1.061	0.050*
$DiffMPH_{SDS}$	Non-DICT	52	−1.27	0.912		76	−1.39	0.944	
	DICT	54	−1.47	0.971	NS	71	−1.50	0.916	NS
GH_{max} AITT/24 h, mU/L	Non-DICT	51	47.87	23.506		75	51.8	24.712	
	DICT	51	47.2	25.165	NS	68	45.99	23.006	NS
IGF-I SDS	Non-DICT	51	−0.62	1.022		74	−0.56	0.981	
	DICT	53	−0.97	1.193	0.05	70	−0.99	1.127	0.005
IGFBP 3 SDS	Non-DICT	51	−0.22	1.090		75	−0.12	1.066	
	DICT	54	−0.23	0.998	NS	71	−0.23	1.070	NS
Ratio IGF-I/IGFBP 3 SDS	Non-DICT	52	−0.70	1.007		76	−0.64	1.002	
	DICT	54	−0.78	0.987	NS	71	−0.80	0.956	NS
Bone age delay, y	Non-DICT	48	−1.50	0.835		69	−1.38	0.915	
	DICT	48	−1.84	0.959	0.029	64	−1.80	0.965	0.008

Nonparametric Mann-Whitney U test was used.
* t test.

growth response was found in both the DICT group ($p <$ 0.028) and the non-DICT group ($p < 0.001$).

First-year growth response for the 58 children in the PP population who remained prepubertal was also analyzed. For children on GH_{33}, a growth response of 0.60 ± 0.22 SDS was found in the DICT group compared with 0.50 ± 0.12 SDS in the non-DICT group ($p = 0.22$; NS). For GH_{67}, the corresponding results were 0.75 ± 0.19 SDS and 0.77 ± 0.24 SDS (NS; Fig. 1). A dose-response relationship with change in $height_{SDS}$ was found in the non-DICT group ($p < 0.004$) and also in the DICT group ($p < 0.036$).

For children in the control group who remained prepubertal during the first year of the study, there were no significant differences between growth during the first year of the study and during the pretreatment year for either the DICT or non-DICT groups: both subgroups continued to grow at a similar rate during the first year of the study to that during the pretreatment year (DICT: −0.04 ± 0.37 SDS first year *versus* 0.09 ± 0.16 SDS pretreatment year; non-DICT: −0.03 ± 0.20 first year *versus* 0.01 ± 0.11 SDS pretreatment year).

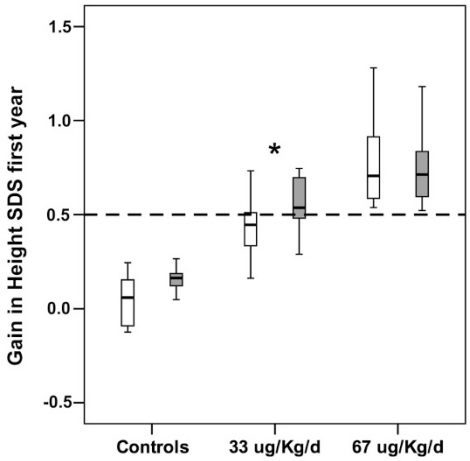

Figure 1. First-year growth response in controls and GH treated, 33 or 67 μg/kg/d in prepubertal ITT population with normal (□) or delayed (■) ICT. *Box* and *whisker* plots show median, interquartile range, and values within ±1.5 of the interquartile range. First-year growth response in the GH_{33} DICT group was significantly higher (*$p < 0.03$) than in the GH_{33} non-DICT group.

The first-year growth response of prepubertal GH_{33} DICT children correlated positively with the 3-mo ($p < 0.043$) and 12-mo IGF-I response ($p < 0.011$). No such correlation was found for the GH_{33} non-DICT individuals. When dividing the study population into children with ISS and those born SGA, results for both subgroups were similar to those for the total group.

FH outcomes. Comparing the effects of GH treatment on FH in the groups revealed that growth response in children receiving GH_{33} for whom timing of the ICT was normal was no better than the response of the control group. For the group with DICT receiving the same GH dose, FH (PP: $p < 0.001$; ITT: $p < 0.023$), $diffMPH_{SDS}$ (PP: $p < 0.018$; ITT: $p < 0.026$), and gain in $height_{SDS}$ from the start of the treatment (PP: $p < 0.001$; ITT: $p < 0.001$) were significantly greater than in controls. When comparing the DICT and non-DICT groups who received GH_{33}, significantly greater outcome in the DICT group relative to the non-DICT group was found: FH (PP: $p < 0.020$; ITT: $p < 0.017$), $diffMPH_{SDS}$ (PP: $p < 0.024$; ITT: $p < 0.029$), and gain in $height_{SDS}$ (PP: $p < 0.004$; ITT: $p < 0.002$). Among the children on GH_{67}, both ICT groups responded with a similar increase in FH_{SDS}, $diffMPH_{SDS}$, and gain in $height_{SDS}$. Furthermore, there was a dose-response relationship for all three outcome variables for the non-DICT but not for the DICT group. In the untreated group, no significant difference in FH outcomes was detected between children with a normal or delayed ICT (Fig. 2; Table 2).

Using linear regression analyses separately for the GH_{33} and GH_{67} of the PP population, each month of delay in ICT for the GH_{33} group corresponded to a gain in FH_{SDS} of 0.13 SDS ($p < 0.03$; Fig. 3). The slope was significant for the GH_{33} group but not for the GH_{67} group. Overall, when not separating the two doses, the slope was significant ($p < 0.003$) and the gain in FH of 0.12 SDS/ICT month.

Outcomes at FH in children with ISS. When children born SGA were excluded from the analysis, none of the outcome variables at FH differed between the DICT and non-DICT children on GH_{67}. However, in GH_{33} all outcomes differed: DICT children were taller (PP: $p < 0.019$; ITT: $p < 0.003$), closer to MPH_{SDS} (PP: $p < 0.023$; ITT: $p < 0.019$), and had gained more height (PP: $p < 0.027$; ITT: $p < 0.003$) than non-DICT children.

The GH_{33} DICT group showed a significant increase in FH (PP: $p < 0.001$; ITT: $p < 0.007$), $diffMPH_{SDS}$ (PP: $p < 0.031$; ITT: $p < 0.067$), and gain in $height_{SDS}$ from the start of the treatment (PP: $p < 0.001$; ITT: $p < 0.001$) relative to controls. The treatment response of the non-DICT individuals on GH_{33} did not differ significantly from those of the controls.

Also when explaining the variance in gain in $height_{SDS}$ with a multivariate analyses, no influence of SGA was found. The gain in $height_{SDS}$ was explained by high/low GH dose ($p < 0.001$), familiar short stature ($p < 0.002$), and DICT ($p = 0.015$) but not by SGA ($p = 0.503$, NS).

IGF-I response. The short-term response of IGF-I after GH treatment was similar in children with non-DICT and DICT (Fig. 4), despite the fact that children with DICT had lower baseline IGF-I levels (Table 1). Levels did not differ significantly at any time point. So, the $IGF\text{-}I_{SDS}$ response did not differ between DICT and non-DICT children.

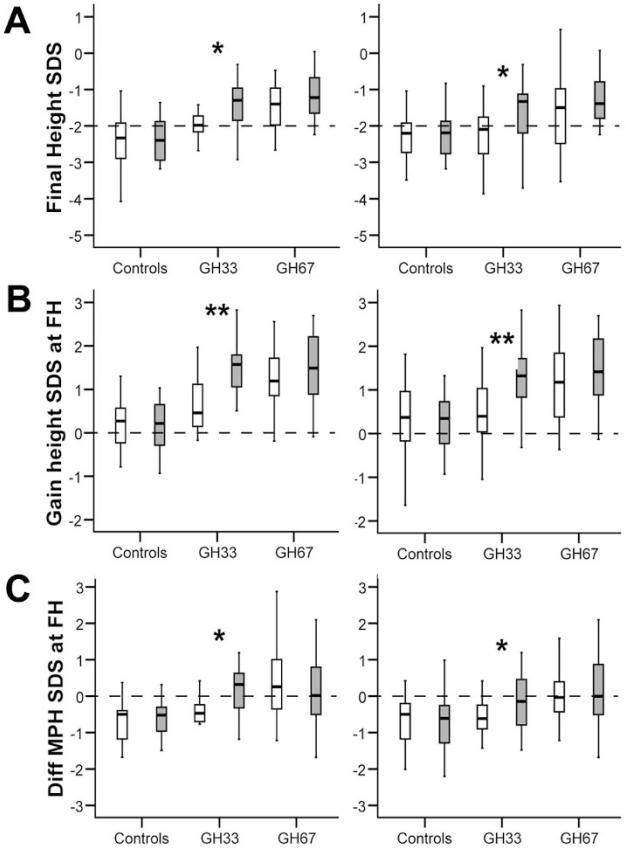

Figure 2. Final height (FH) outcomes in PP. PP population (*left*) and ITT population (*right*) as FH_{SDS} (*A*), gain in $height_{SDS}$ (*B*), and difference between FH_{SDS} and midparental $height_{SDS}$ ($diffMPH_{SDS}$) (*C*) in groups with normal (non-DICT, □) or delayed (DICT, ▩) ICT. *Box* and *whisker* plots show median, interquartile range, and values within ±1.5 of the interquartile range. * and ** represent significant differences between DICT and non-DICT subjects in the GH_{33} group on <0.03 and <0.005 p levels, respectively. Analyzing the dose response in DICT and non-DICT, dose response were significant ($p < 0.03$). Furthermore, comparing outcomes in the GH_{67} group with controls, all outcomes were significantly better in the GH_{67} group. When comparing outcomes between controls and GH_{33} group, only the DICT group responded better than controls (p levels <0.05 in all comparisons).

DISCUSSION

The controversy over the use of GH treatment in short non-GHD children has been based on ethical and cost-efficacy considerations. Characterizing subgroups of patients so far included in the ISS group that respond predictably to GH is of significant clinical interest. The identification of delayed age at ICT as a factor contributing to short stature in many children brings a new perspective into the discussion. As we previously reported, nearly half of individuals with ISS can be categorized as having DICT (2), and the number of individuals that this study applies to is quite substantial. Here, we show that DICT children respond to standard GH dose, whereas children with normal ICT need higher GH dose. Previously, it has been reported that a delay in ICT was associated with a dysfunctional GH-IGF-I axis (2,3,15). We now report from a

Table 2. *Final growth outcome for all or only ISS children with normal (Non-DICT) and delayed ICT (DICT) in the per-protocol (PP) and the intention-to-treat (*ITT*) populations (panels)*

	Controls (C)		GH_{33}			GH_{67}		$p <$		Dose reponse
	n	Mean ± SD	*n*	Mean ± SD	*p*(d) <	*n*	Mean ± SD	C *vs* GH_{33}	C *vs* GH_{67}	GH_{33} *vs* GH_{67}
All PP										
Non-DICT										
Final height SDS	17	−2.44 ± 0.985	15	−1.98 ± 0.52	NS	20	−1.46 ± 0.899	NS	0.003	0.028
Diff MPH, FH	17	−0.70 ± 0.568	15	−0.65 ± 1.038	NS	20	0.33 ± 1.164	NS	0.001	0.008
Gain SDS at FH	17	0.16 ± 0.772	15	0.64 ± 0.637	NS	20	1.21 ± 0.721	NS	0.001	0.028
DICT										
Final height SDS	12	−2.33 ± 0.646	17	−1.42 ± 0.75	0.020	25	−1.26 ± 0.828	0.001	0.001	NS
Diff MPH, FH	12	−0.60 ± 0.789	17	0.15 ± 0.713	0.024	25	0.17 ± 0.933	0.018	0.014	NS
Gain SDS at FH	12	0.16 ± 0.586	17	1.41 ± 0.710	0.004	25	1.57 ± 0.771	0.001	0.001	NS
All ITT										
Non-DICT										
Final height SDS	25	−2.38 ± 0.847	22	−2.24 ± 0.681	NS	29	−1.65 ± 0.916	NS	0.005	0.011
Diff MPH, FH	25	−0.65 ± 0.780	22	−0.74 ± 0.922	NS	29	0.10 ± 1.087	NS	0.003	0.002
Gain SDS at FH	25	0.36 ± 0.811	22	0.50 ± 0.704	NS	29	1.18 ± 0.857	NS	0.001	0.009
DICT										
Final height SDS	18	−2.15 ± 0.785	21	−1.66 ± 0.923	0.017	32	−1.36 ± 0.875	0.023	0.001	NS
Diff MPH, FH	18	−0.57 ± 0.846	21	−0.06 ± 0.786	0.029	32	0.15 ± 0.997	0.026	0.005	NS
Gain SDS at FH	18	0.43 ± 0.958	21	1.24 ± 0.743	0.002	32	1.47 ± 0.782	0.001	0.001	NS
ISS PP										
Non-DICT										
Final height SDS	10	−1.97 ± 0.870	8	−1.93 ± 0.280	NS	16	−1.37 ± 0.944	NS	0.077	0.023
Diff MPH, FH	10	−0.57 ± 0.550	8	−0.58 ± 0.418	NS	16	0.25 ± 1.266	NS	0.027	0.013
Gain SDS at FH	10	0.55 ± 0.620	8	0.66 ± 0.736	NS	16	1.24 ± 0.737	NS	0.031	0.016
DICT										
Final height SDS	10	−2.41 ± 0.626	16	−1.32 ± 0.663	0.019	22	−1.32 ± 0.854	0.000	0.001	NS
Diff MPH, FH	10	−0.62 ± 0.868	16	0.09 ± 0.69	0.023	22	0.16 ± 0.975	0.031	0.039	NS
Gain SDS at FH	10	0.10 ± 0.565	16	1.46 ± 0.693	0.027	22	1.50 ± 0.783	0.000	0.000	NS
ISS ITT										
Non-DICT										
Final height SDS	15	−2.07 ± 0.773	12	−2.19 ± 0.647	NS	19	−1.43 ± 0.900	NS	0.021	0.004
Diff MPH, FH	15	−0.65 ± 0.624	12	−0.61 ± 0.421	NS	19	0.19 ± 1.165	NS	0.006	0.003
Gain SDS at FH	15	0.68 ± 0.61	12	0.48 ± 0.774	NS	19	1.15 ± 0.750	NS	0.060	0.032
DICT										
Final height SDS	15	−2.13 ± 0.815	18	−1.39 ± 0.657	0.003	28	−1.46 ± 0.862	0.007	0.007	NS
Diff MPH, FH	15	−0.53 ± 0.907	18	0.00 ± 0.699	0.019	28	0.08 ± 1.012	0.067	0.067	NS
Gain SDS at FH	15	0.49 ± 0.993	18	1.38 ± 0.694	0.003	28	1.37 ± 0.783	0.001	0.001	NS

Children born SGA are included in the two *upper panels* and excluded from the two *lower panels*. *p*(d) denotes *p* values when comparing DICT and Non-DICT individuals. All other comparisons are between groups. Nonparametric Mann-Whitney *U* test was used.

randomized, controlled study that children treated with standard-dose GH (33 μg/kg/d) with DICT respond better than non-DICT children. In addition, FH of non-DICT children receiving GH_{33} did not differ significantly from FH in the untreated control group. This raises the question of whether previous reports showing nonresponse to this dose of GH therapy in children with ISS may be related to a (nonobserved) selection bias toward non-DICT children.

Two methodological issues deserve consideration. Contemporary studies distinguish subjects with ISS born AGA from short children born SGA. As this study was initiated before the distinction was identified between ISS and short children born SGA (17), the present report included a subgroup of short children born SGA with incomplete catch-up growth. We have previously shown that the response to GH therapy is similar in short SGA children and ISS children when adjusted for their pretreatment auxology (10,11), and hence we find it acceptable to report them as a joint group. In fact, the results of this study show similar results independent of being born AGA or SGA: DICT children being more GH responsive and also being the only group to gain height on GH_{33}. Although this study was not designed with the current *post hoc* analysis in mind, the sample turned out to be well balanced, with 52 non-DICT and 54 DICT children in the PP population and 76 non-DICT and 71 DICT children in the ITT population. The same was true for the three treatment groups (Table 2). Despite these limitations, the results prove the concept of ICT-dependent growth in response to GH therapy.

Conventional teaching of growth patterns holds that crossing percentile curves during the first 2–3 y of life is acceptable (finding one's growth channel). In previous reports, our prediction models included early growth (0–2 y) as a parameter for predicting the growth response to GH treatment (9–12), and we found that early growth patterns (*i.e.* loosing length or keeping relative length) are as a strong predictor of FH as IGF-I levels or GH_{max} during provocation tests (9). Modeling such growth patterns by the ICP method suggests that "finding one's channel" happens around the ICT. Our analyses show for the first time that children with DICT had a better long-term height gain and FH after a standard low GH dose than

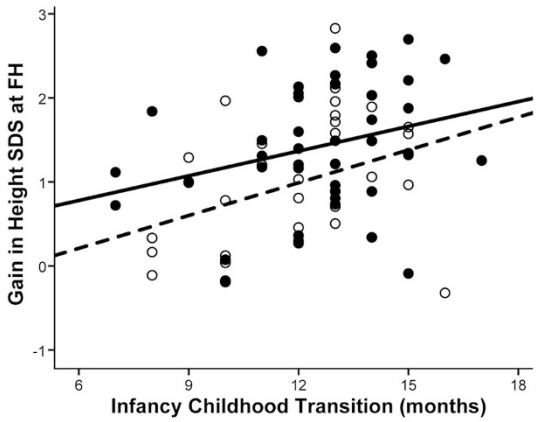

Figure 3. Age (mo) at the ICT in relation to gain in height$_{SDS}$ from study start to final height (FH) for the GH-treated children of the PP population according to GH dose: (●) = 67 μg/kg/d (*solid line*) and (○) = 33 μg/kg/d (*dotted line*). The slope was significant for GH_{33} but not for GH_{67}. The GH_{33} height gain per ICT month was 0.13 SDS (95% CI: 0.02–0.25; $p < 0.03$). Overall, when combining the gain in height$_{SDS}$ results from GH_{33} and GH_{67}, the slope was significant, 0.12 SDS/mo (95% CI: 0.04–0.20; $p < 0.003$). Similar results were obtained in the ITT population, where the gain per month in GH_{33} was 0.14 (95% CI: 0.04–0.25; $p < 0.010$).

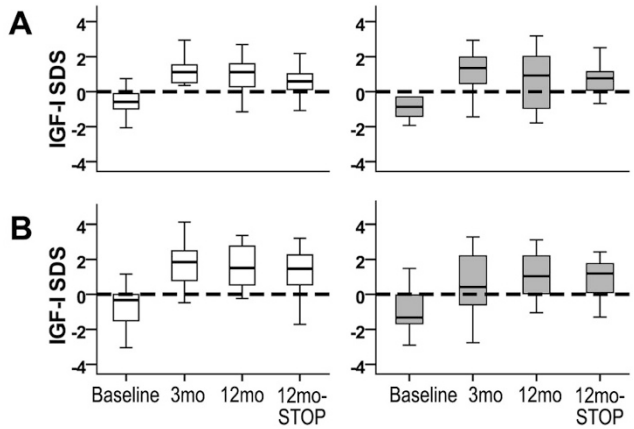

Figure 4. IGF-I$_{SDS}$ at baseline, at 3 and 12 mo, and the mean from 12 mo until GH stop in the PP population with normal (*left,* non-DICT □) or delayed (*right*, DICT ■) ICT according to GH dose 33 μg/kg/d (*A*) or 67 μg/kg/d (*B*). *Box* and *whisker* plots show median, interquartile range, and values within ± 1.5 of the interquartile range. No significant differences between DICT and non-DICT treated subjects were observed. Furthermore, the IGF-I levels did not differ significantly between the dose groups.

children with a normal ICT. Children with DICT gained an average of 1.4 SD (9 cm) in FH when receiving the lower GH dose, whereas non-DICT children gained 0.64 SD (4 cm). The latter was not significantly different from the gain in untreated controls. With each month of ICT delay, the GH-induced height gain to FH increased by 0.13 SDS. Thus, we propose that retarded growth velocity during the first 0–2 y of life can be a significant signal of disturbed GH/IGF-I axis activity, challenging conventional teaching about crossing channels during this period of life being acceptable.

Retarded growth in early life should not be confused with constitutional delay of growth and puberty, with a normal growth rate during early life and childhood that slows down around juvenility, and lack signs of puberty at an age of 2 SD above the mean chronological age for puberty onset (3). In this study, analysis of the timing of puberty showed comparable ages both at onset of puberty and when FH was reached for DICT and non-DICT children. This allowed us to reject the constitutional delay of growth and puberty (CDGP) hypothesis as a reason for the height gain in our study group.

In conclusion, in this controlled clinical trial in which the children were randomized to a low-standard (33 μg/kg/d) or high (67 μg/kg/d) GH dose, children with DICT had both a greater short-term and long-term growth response to standard-dose GH treatment than children with a normal ICT. The latter group of children required a higher GH dose to achieve similar gain in height. As such, there is a rationale for using standard-dose GH therapy for children with DICT and high-dose therapy for children with a normal timing of ICT.

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