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Does skeletal disproportion in children with idiopathic short stature influence response to growth hormone therapy?

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Disclosure

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Background

- Children with idiopathic short stature (ISS) have an array of causes that lead to short stature and/or poor growth velocity[1].
- Genetic causes of short stature, notably SHOX mutations, can be associated with subtle skeletal disproportion with shorter limbs.
- We hypothesized that children with ISS and skeletal disproportion have a diminished growth response to growth hormone (GH) treatment compared to children with proportionate short stature.

Methods

- Participants were ISS patients registered in Pfizer International Growth Database (KIGS) with a stimulated peak GH >10 µg/L and treated with GH.
- Growth responses were analyzed after 1 year (short-term) and at near-adult height (long-term).
- Sitting height % SDS was grouped as:
  - *normal* (-1.0 to ≤1.0)
  - *mild skeletal disproportion* (1.0 to <2.1)
  - *moderate skeletal disproportion* (>2.1)
- Wilcoxon rank sum test was used for univariate statistical comparisons. ANOVA was used for group comparisons. P-value < 0.05 was considered significant.

Results

- Prior to GH treatment, the ISS group displayed Gaussian distribution for skeletal proportion.
- For short-term analyses, the number of patients in each group was: normal (193), mild (201), and moderate (130) skeletal disproportion.
- Short-term growth responses, expressed as Studentized Residuals using the KIGS ISS 1st-year prediction model showed a trend toward poorer growth response with greater severity of disproportion (mean values; normal = -0.04, mild = -0.17, and moderate = -0.25; p=0.07).
- Number of patients in each group attaining near-adult height was: normal (57), mild (52), and moderate (28).
- Long-term growth showed a larger difference, expressed as Δ height SDS from GH start to near-adult height (mean values; normal/mild = 1.75 vs moderate = 1.42, p<0.05)

Summary

- Children with ISS and moderate skeletal disproportion have reduced long-term height response to GH compared to those without disproportion, suggesting subtle GH resistance in the former.

Table 1. Characteristics of the population studied 1 year after GH treatment, according to level of skeletal disproportion.

		Normal (girls=59; boys=134)			Mild (girls=56; boys=145)			Moderate (girls=30; boys=100)		
Background		**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Birth weight SDS		193	-0.49	0.83	201	-0.50	0.93	130	-0.65	0.88
Max GH peak µg/L		193	16.3	9.3	201	16.8	9.2	130	17.5	7.8
Mid-parental height SDS		192	-1.17	1.27	200	-1.32	1.00	128	-1.62	1.04
Start of GH treatment										
Chronological age (years)		193	8.3	2.6	201	8.5	2.5	130	8.6	2.4
Bone age delay (years)		91	1.8	1.2	104	2.0	1.2	57	1.9	1.2
Height SDS	*	**193**	**-2.78**	**0.70**	**201**	**-2.95**	**0.67**	**130**	**-3.22**	**0.78**
Sitting height SDS		193	-3.14	0.81	201	-2.67	0.68	130	-2.40	0.85
Sitting height % SDS	*	**193**	**0.36**	**0.46**	**201**	**1.49**	**0.30**	**130**	**2.82**	**0.67**
BMI SDS		193	-0.75	0.96	201	-0.47	0.90	130	-0.17	1.18
1-year of GH therapy										
Height velocity (cm/year)		193	8.1	1.5	201	8.0	1.8	130	7.8	1.6
Height SDS		193	-2.12	0.70	201	-2.31	0.73	130	-2.59	0.80
Δ height SDS	NS	**193**	**0.66**	**0.29**	**201**	**0.64**	**0.31**	**130**	**0.63**	**0.30**
Sitting height SDS		167	-2.33	0.82	172	-2.02	0.87	110	-1.80	0.88
Sitting height % (SDS)		187	0.62	0.75	172	1.49	0.73	110	2.57	0.99
Δ SH % SDS		167	0.22	0.83	172	-0.00	0.68	110	-0.25	0.85
Mean dose (mg/kg/week)		193	0.23	0.06	201	0.23	0.06	130	0.22	0.06
ISS prediction model										
Predicted HV (ISS model)		153	8.2	0.8	156	8.4	0.9	105	8.1	1.0
Actual height velocity (cm/year)		153	8.2	1.4	156	8.2	1.8	105	7.8	1.6
Studentised Residuals (ISS)	NS	**153**	**-0.04**	**1.05**	**156**	**-0.17**	**1.18**	**105**	**-0.25**	**1.16**

**** = p< 0.05, NS = Not Significant***

Table 2. Characteristics of the population treated with GH and studied at near-final height, according to level of skeletal disproportion.

		Normal (girls=20; boys=37			Mild (girls=13; boys=39			Moderate (girls=4; boys=24		
Background		**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Birth weight SDS		57	-0.30	0.85	52	-0.33	0.84	28	-0.63	1.11
Max GH peak µg/L		57	14.6	6.0	52	15.3	5.5	28	14.2	3.7
Mid-parental height SDS		56	-1.07	1.12	52	-0.86	0.91	28	-1.56	1.07
Start of GH treatment										
Chronological age (years)		57	8.9	2.3	52	9.0	2.1	28	8.9	2.5
Bone age delay (years)		30	1.6	1.2	25	2.0	1.0	15	1.8	1.1
Height SDS	NS	**57**	**-2.69**	**0.68**	**52**	**-2.65**	**0.59**	**28**	**-2.87**	**0.62**
Sitting height SDS		57	-3.02	0.75	52	-2.38	0.56	28	-2.00	0.70
Sitting height % SDS	*	**57**	**0.36**	**0.43**	**52**	**1.49**	**0.32**	**28**	**2.86**	**0.70**
BMI SDS		57	-0.75	1.04	52	-0.50	0.76	28	-0.37	0.81
At near-adult height										
Chronological age (years)		57	17.7	1.5	52	17.5	1.3	28	17.7	1.4
Height SDS	*	**57**	**-0.95**	**0.92**	**52**	**-0.89**	**0.87**	**28**	**-1.45**	**0.84**
Δ height SDS (NAH-start)	NS	**57**	**1.73**	**0.77**	**52**	**1.76**	**0.71**	**28**	**1.42**	**0.61**
Sitting height SDS		57	-0.94	1.01	52	-0.32	1.06	28	-0.29	1.04
Sitting height % (SDS)	*	**57**	**0.78**	**0.99**	**52**	**1.59**	**0.75**	**28**	**2.75**	**1.19**
Δ SH % SDS (NAH-start)	*	**57**	**0.41**	**1.00**	**52**	**0.10**	**0.75**	**28**	**-0.11**	**0.89**
Mean dose (mg/kg/week)		57	0.25	0.05	52	0.25	0.05	28	0.24	0.05

References: Fletchner 2014 and 2) Malaquias AC. Horm Res Paediatr. 2013;80(6):449-56 2013

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