The growth response to growth hormone treatment is greater in patients with *SHOX* enhancer deletions compared to *SHOX* defects

S.H. Donze[1], C.R. Meijer[1], S.G. Kant[2], G.R.J. Zandwijken[3], A.H. van der Hout[4], R.M.L. van Spaendonk[5], A.M.W. van den Ouweland[6], J.M. Wit[1], M. Losekoot[2], W. Oostdijk[1]

Departments of [1] Pediatrics and [2] Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands, [3]Dutch Growth Research Foundation, Rotterdam, The Netherlands, Departments of Clinical Genetics of [4] University Medical Center Groningen, Groningen, [5] VU Medical Center, Amsterdam and [6] Erasmus Medical Center, Rotterdam, The Netherlands

Conclusions

Patients with *SHOX* enhancer deletions are equally short, but less disproportionate than patients with *SHOX* haploinsufficiency, and show a greater first year response to growth hormone

Background

Heterozygous *SHOX* defects cause Léri-Weill Dyschondrosteosis

- Deletions in down- or upstream enhancer regions of *SHOX* (SED) show clinical picture similar to *SHOX* haploinsufficiency (SHI)
- Pathogenicity of *SHOX* duplications (SDUP) is uncertain

Growth Hormone (GH)

- On GH treatment significant increase in height SDS during first 2 years in children with SHI (Blum et al. JCEM 2007)

Aim

To describe the clinical characteristics and growth response to GH treatment in patients with aberrations of *SHOX* and its enhancers.

Methods

Retrospective, multi-centre, observational study in 88 children, aged 2-16 years, and their parents. Information on linear growth from 33 prepubertal GH-treated patients was collected up to 4 years.

Results

Phenotypic characteristics

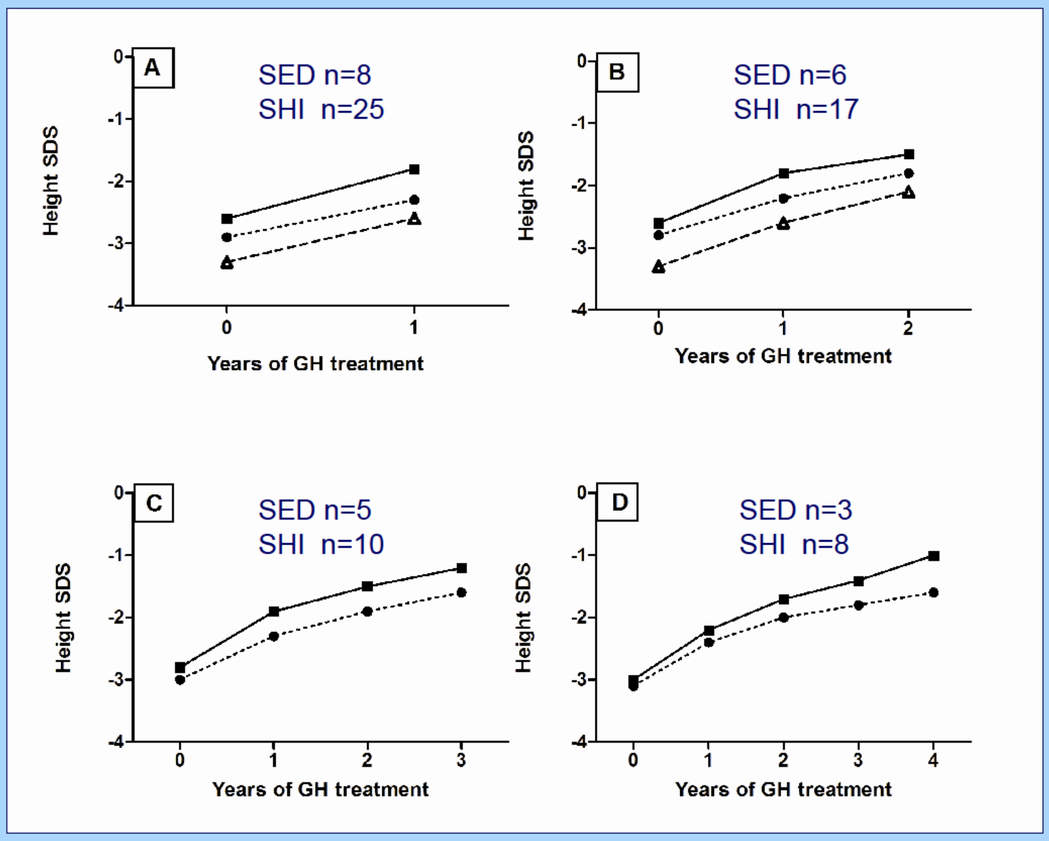
- Similar height SDS, patients with SEDs were less disproportionate
- Madelung deformity in 31%, similar in SHI and SEDs (p=0.11)
- In 8 children with SDUP: height SDS -3.5 to -2.2, SH/H SDS 0.7 to 1.9. Height SDS affected parents: -2.5 to 1.2, unaffected parents: -3.5 to -0.5

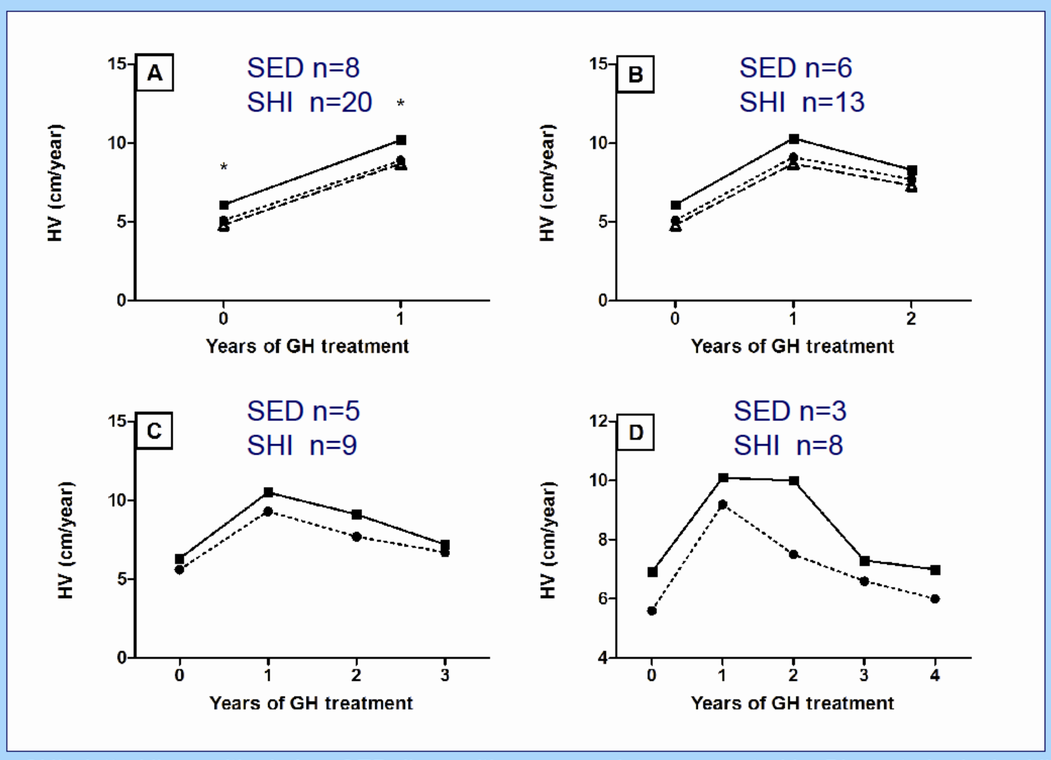
Clinical characteristics at first visit in patients with *SHOX* mutations and deletions and *SHOX* enhancer deletions

	SHI		SEDs		
	N		N		p
Age at first visit (yrs)	54	8.3 (3.5)	26	8.5 (3.7)	0.839
Male/female		23/31		11/15	0.981
Birth weight SDS	43	-0.4 (1.3)	23	-0.3 (1.3)	0.728
Birth Length SDS	23	-1.0 (1.2)	14	-1.1 (1.4)	0.823
Height SDS	54	-2.6 (0.8)	26	-2.3 (0.8)	0.111
Target Height SDS	50	-1.0 (0.6)	24	-0.9 (0.5)	0.647
SH/H SDS	50	3.2 (1.1)	22	1.9 (1.3)	**<0.01**
Armspan/height ratio	21	0.95 (0.03)	12	0.96 (0.03)	0.365
BMI SDS	51	0.5 (0.9)	25	0.1 (1.1)	0.069
Extremities-trunk ratio	21	2.43 (0.2)	11	2.57 (0.2)	**0.028**
Height SDS affected parent	28	-2.4 (0.9)	21	-1.9 (0.9)	**0.032**
SH/H SDS affected parent	9	3.3 (1.4)	14	2.3 (1.8)	0.168

Response to Growth Hormone

- First year delta height SDS, HV and HV SDS significantly greater in prepubertal children with SEDs
- Serum IGF-I SDS increased similarly in SHI and SED, no effect of GH on bone maturation or body proportions





SHI: dotted lines with circles, SED: lines with squares, data as reported by Blum et al.: dashed lines with triangles. Statistically significant differences are indicated with an asterisk.

Discussion

- Remarkable heterogeneity of statural growth and body disproportion
- Speculations on greater response to GH in SEDs: 1. GH promotes expression of *SHOX (*via downstream GH-dependent transcription factors). Two intact functional copies of *SHOX* in SEDs → greater response to GH, 2.*SHOX* deficiency is less severe in patients with SEDs
- The recommended GH dose for SHI as reported by Blum et al. is efficacious in both SHI and SED
- Pathogenicity of SDUPs remains unclear: no body disproportion in all children, no clinical features in their parents

For further details: Donze et al., European Journal of Endocrinology 2015; forthcoming

ESPE 2015 81--P1

GH and IGF Treatment

Stephany Donze

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com