Effects of 8 years of growth hormone treatment on scoliosis in children with Prader-Willi syndrome

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Abstract

Context: Scoliosis is frequently seen in children with Prader-Willi syndrome (PWS). There is still concern that growth hormone (GH) treatment might increase the risk of onset or progression scoliosis. Short-term data suggested no adverse effects of GH treatment on scoliosis, but the long-term effects of GH treatment on the development of scoliosis in PWS are unknown.

Objective: To investigate the effects of 8 years of GH treatment on scoliosis in children with PWS.

Design: Open-label, prospective cohort study. Spine X-rays and DEXA-scans were annually performed.

Setting: Dutch PWS Reference Center.

Patients: 103 children with PWS receiving GH treatment and 23 age-matched GH-untreated children with PWS.

Intervention: Eight years of treatment with 1mg GH/m2/day (~0.035mg/kg/day).

Main outcome measures: Prevalence and severity of scoliosis after 8 years of GH treatment versus controls.

Results: After 8 years of GH treatment, at median age of 10.8 years, the prevalence of scoliosis was 77.7%. No difference in prevalence or severity of scoliosis was found between GH-treated and age matched untreated children with PWS. Height SDS and trunkLBM were significantly higher in GH-treated children. Higher bone mineral density of the lumbar spine (BMD_{LS} SDS) and bone mineral apparent density of lumbar spine ($BMAD_{LS)}$ SDS were associated with a lower Cobb angle (r=-0.270, p=0.008).

Conclusions: GH treatment has on the long-term no adverse effects on the prevalence and severity of scoliosis in children with PWS. As $BMAD_{LS}$ SDS is inversely associated with Cobb angle, it is pivotal to optimize BMD-status in children with PWS.

Introduction

Prader-Willi syndrome (PWS) is a rare syndrome caused by the lack of expression of the paternally derived chromosome 15q11-q13, caused by a paternal deletion, maternal uniparental disomy (mUPD), and in rare cases by an imprinting center defect (ICD) or paternal chromosomal translocation[1,2]. Clinical findings characterizing PWS are developmental delay, muscular hypotonia, behavioral problems, hyperphagia with obesity and short stature [2–5]. Hypothalamic dysfunction may be responsible for many features of PWS[6,7].

Scoliosis is frequently seen in children and adults with PWS. The reported prevalence of scoliosis in children with PWS varies between 32.1% and 86%[8–12]. In comparison, the prevalence of scoliosis in the general Dutch adolescent population is 2.7%[13]. Children with PWS can exhibit two types of scoliotic curves. Long C-curve scoliosis (LCS) is mostly seen in young children with PWS. This type of curve is due to the underlying hypotonia and also found in children with neuromuscular disorders causing hypotonia. Later in childhood, the curve may convert to an S-shaped scoliosis, defined as idiopathic scoliosis (IS)[14]. (Figure 1)

Scoliosis and scoliosis treatment have a significant impact on the quality of life of children with PWS. Physical therapy plays an important role in the prevention and treatment of scoliosis. Hypotonia, as seen in children with PWS, has been associated with the development of scoliosis and creating more muscle mass may prevent the development and progression of scoliosis. Treatment options of scoliosis are brace treatment or surgery[15].

Growth hormone (GH) treatment is a registered treatment for children with PWS since 2000. It improves body composition, psychomotor development and cognition in children with PWS[16–20]. Because GH treatment induces catch-up growth in height, there have been concerns about development of scoliosis or worsening of an existing scoliosis. However, our previous randomized controlled study of 2-years of GH treatment in children with PWS

showed no significant difference between GH-treated children and untreated controls with regard to the onset of scoliosis, curve progression and start of the scoliosis treatment[14]. Other studies found similar findings[21–23]. GH treatment increases lean body mass, which may counteract the adverse effects of accelerated growth on scoliosis.

Although previous studies were reassuring for the short-term effects of GH treatment on scoliosis, the long-term effects of GH treatment on scoliosis are still unknown. The aim of this study was to investigate the long-term effect of GH treatment on the prevalence and severity of scoliosis in children with PWS. The secondary objectives were to assess if the age at start of GH treatment and the amount of lean body mass or the bone mineral density are correlated with development of scoliosis. We hypothesized that the prevalence of scoliosis in children with PWS after 8 years of GH treatment would be similar to the prevalence in non-GH-treated children with PWS.

Methods

Patients

All participants were diagnosed with PWS, confirmed by methylation pattern analysis of the PWS region, and participated in the Dutch PWS Cohort study[24,25]. All children were studied from the start of their GH treatment and all started GH treatment before the 1st of July 2011. At the start of GH treatment, all children were prepubertal, defined as a Tanner breast stage < 2 for girls and testicular volume < 4 ml for boys[26]. Those who reached adult height within less than 8 years after GH treatment start were excluded from present study, as GH dosage was lowered after attainment of adult height. For our control group, we included age-matched children with PWS, who were prior to treatment with GH.

Design

Prospective study investigating the long-term effects of GH-treatment in children with PWS. All children in the GH-group were treated with 1.0mg GH/m2 (~0.035mg/kg) once daily for 8

consecutive years. During each visit, the GH dose was adjusted to the calculated body surface area.

Children visited the Dutch PWS Reference Center in Rotterdam and received multidisciplinary care from the PWS team, which included regular follow-up by an orthopaedic surgeon. The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Center. Written informed consent was obtained from parents and children older than 12 years. Assent was obtained from children younger than 12 years.

Radiographics

At the start of GH-treatment and every year thereafter, standardized X-rays of the spine were taken. For the GH-treated children, the X-rays before start of GH treatment and at 8 years thereafter were used for analysis. For the control-group, the X-ray before start of GH treatment was used. X-rays were taken in supine position in young children who were too hypotonic to stand. The majority of X-rays were taken at the Erasmus University Medical Center. Some X-rays were performed in other medical centers in The Netherlands, but these were send to the Erasmus Medical Center, where they were assessed. In ten cases, the 8-year X-ray was not available, in those cases the X-ray closest in time to the 8 years was used (max. 1 year below or 2 years above the 8-year X-ray).

To diagnose scoliosis, the Cobb angle was measured on a posterior-anterior or anterior-posterior x-ray of the complete spine. The Cobb angle is the angle between the most tilted upper and most tilted lower vertebra contained in the curve and is measured between the cranial endplate of the upper vertebra and caudal endplate of the lower vertebra[27]. Normally, there is no measurable deviation. Scoliosis is defined as a spinal curve with a Cobb angle of more than 10º. Cobb angles were measured by two independent trained observers. The interobserver variation was minimal (mean (SD) difference -0.07º (2.5), intraclass coefficient (ICC) = 0.995, $p < 0.001$). In addition to these measurements, an orthopaedic surgeon,

specialized in spine disorders (J.R.), measured Cobb angles in a random sample (ICC = 0.983, p <0.001).

Anthropometrics

Standing height was measured with a Harpenden Stadiometer and supine length with a Harpenden Infantometer (Holtain Ltd., Crosswell, UK). Weight was measured on a calibrated scale (Servo Balance KA-20-150S; Servo Berkel Prior, Katwijk, the Netherlands). Height, weight and body mass index (BMI) standard deviation scores were calculated with Growth Analyser RCT 4.1 (www.growthanalyser.org), based on Dutch Reference values[28,29].

Dual energy x-ray absorptiometry

Dual energy x-ray absorptiometry (DXA) (Lunar Prodigy type; GE healthcare, Chalfont St. Giles, UK) was annually performed in all children to measure lean body mass (LBM), fat percentage, bone mineral density of the lumbar spine (BMD_{LS}) and bone mineral density of the total body (BMD_{TB} SDS). The DXA-machine was calibrated daily. To analyse the effects of GH treatment on relative muscle mass, a ratio of trunkLBM vs. body surface area (BSA) ratio (trunkLBM:BSA) was used, as previously described[8]. FM% SDS was calculated according to age- and sex-matched Dutch reference values[30]. As the BMD_{LS} is underestimated by the areal presentation, we corrected for bone size by calculating the bone mineral apparent density of the lumbar spine ($BMAD_{LS}$). The model $BMAD_{LS} = BMD_{LS} \times [4/(\pi \times \text{width})]$ was used, with width as the mean width of the second to fourth lumbar vertebral bodies[31]. BMD_{TB} SDS and $BMAD_{LS}$ SDS were calculated to age-matched and sex-matched reference values of the Dutch population[32].

Assay

Fasting blood samples were collected for assessment of serum IGF-1 levels. All blood samples were measured in the Biochemical and Endocrine laboratories of the Erasmus

University Medical Center, Rotterdam. Because serum IGF-1 levels are age- and sex-dependent, the values were transformed to SDS values, based on the Dutch population[33].

Statistics

Statistical analysis was performed with SPSS 24.0 (SPSS INC, Chicago, IL). As not all data were normally distributed, non-parametric tests were used and data expressed as median (interquartile range (IQR)). Mann-Withney U tests were used for differences between the GH-treated- and the untreated group, regarding height SDS, weight SDS, age, Cobb angle, IGF-1 SDS and TrunkLBM:BSA ratio. Chi square tests were used to analyse differences in gender, genetic subtype and treatment for scoliosis. Mann-Withney U tests and chi square tests were used to compare the group with and without scoliosis after 8 years of GH treatment. Spearman's Rho was used to analyse correlations between Cobb angle and age of start of GH treatment, serum IGF-1 SDS, sex, genotype, trunkLBM:BSA, $BMAD_{LS}$ SDS and BMD_{TS} SDS of the GH-treated group. Severe scoliosis was set at a Cobb angle > 25º. All children with brace treatment or surgery for their scoliosis were included in the group with Cobb angle > 25º. Pubertal stage was defined as prepubertal (testes volume < 4ml for boys and Tanner breast stage < 2 for girls), early pubertal (testes volume 4-10ml for boys and tanner breast stage 2-3 for girls) or late pubertal (testes volume > 10ml for boys and Tanner breast stage ≥ 4 for girls)[26]. Level of significance was set at a p-value of 0.05.

Results

Clinical characteristics

137 children started GH treatment before the 1st of July 2011. Of these children, 34 were excluded from analyses: 4 were lost to follow-up and 30 reached adult height within the 8 years after start of GH treatment. In total, 103 children completed at least 8 years of continuous GH treatment and were thus eligible for the evaluation of 8 years of GH treatment. The GH-untreated group consisted of 23 age-matched children with PWS, prior to start of GH treatment.

Table 1 shows the clinical characteristics of the GH-treated and untreated group. Of the 103 GH-treated children, 53 were males and 50 females. In the untreated group, 10 were males and 13 females. At the start of GH treatment, the median (IQR) age was 2.8 (1.3; 5.9) years. The median (IQR) trunkLBM:BSA at start of GH treatment was 7.2 (6.8; 7.7) and the median (IQR) Cobb angle 10.3º (7.1; 13.0).

Effect of 8 years of GH treatment on scoliosis in children with PWS

Table 2 shows scoliosis measurements, anthropometrics, and body composition in children with PWS after 8 years of GH compared to age-matched untreated children with PWS. The median (IQR) age of the GH-treated children after 8 years of GH treatment and the untreated children was similar, being 10.81 (9.27; 13.76) vs. 11.4 (9.7;13.35) years (p=0.912), respectively. The GH-treated children were significantly taller compared to the untreated group (p<0.001). After 8 years of GH treatment, 49 children (47.6%) were still prepubertal, compared to 18 children (78.3%) in the untreated group (p = 0.020). As expected, serum IGF-1 SDS was significantly higher in the GH-treated children (p=0.023). Median (IQR) BMD_{TB} SDS, $BMAD_{LS}$ SDS and fat mass % SDS were not different between the groups. Median (IQR) trunkLBM:BSA ratio was higher in GH-treated children than in GH-untreated children (8.83 (8.13; 9.66) and 8.16 (7.40; 8.62) (p=0.001), respectively).
Median (IQR) Cobb angle in the GH-treated group was 18.0º (10.5; 30.0) and 15.0º (7.5; 32.0) in the GH-untreated group, which was not significantly different (p=0.232). The prevalence of scoliosis was not different between the groups, being 77.7% in the GH-treated group and 69.6% in the untreated group (p=0.409). The prevalence of more severe scoliosis (Cobb angle > 25º) and scoliosis treatment was also similar between the groups.

Scoliosis compared to no scoliosis after 8 years of GH treatment

Table 3 presents the data of children who had developed scoliosis after 8 years of GH treatment compared to those who did not. The median (IQR) age at the start of GH treatment did not differ between the groups, being 2.96 years (1.32; 6.12) in the group who developed

scoliosis during 8 years of GH treatment and 2.51 years (1.55; 4.56) in the group without scoliosis after 8 years of GH treatment. No difference in sex, genotype or pubertal stage was found between the groups. The median (IQR) height in the group with scoliosis was -0.02 SDS (-0.88; 0.69) and in the group without scoliosis 0.78 SDS (-0.84; 1.67) (p=0.051). The median (IQR) BMD_{TB} SDS was lower in the children who developed scoliosis compared to those without scoliosis (-0.56 (-1.40; 0.37) vs. 0.14 (-1.01; 1.13), resp. (p=0.036)). The median $BMAD_{LS}$ SDS tended to be lower in children with scoliosis (p=0.054). Serum IGF-1 SDS, vitamin D level, trunkLBM:BSA ratio, BMI SDS, and fat% SDS were not different between GH-treated children with or without scoliosis.

Influence of clinical characteristics on scoliosis in children after 8 years of GH treatment

Twelve children (11.6%) of the GH-treated group were treated with bracing therapy or surgery for their scoliosis. Gender or genotype did not significantly differ between the children who needed scoliosis treatment versus those who did not (data not shown). Serum IGF-1 SDS and age at start of GH treatment were not associated with Cobb angle after 8 years of GH treatment (p>0.79). No difference in Cobb angle was found for sex, genotype, or pubertal stage (data not shown). No correlation was found between height SDS and trunkLBM:BSA and Cobb angle (data not shown). BMD_{TB} SDS was not associated with Cobb angle (r=-0.186, p=0.066). $BMAD_{LS}$ SDS was inversely associated with Cobb angle after 8 years of GH (r=-0.270, p=0.008).

Discussion

This is the first long-term study investigating the prevalence and severity of scoliosis after 8 years of continuous GH treatment in a large group of 103 children with PWS. The results demonstrate that there is no difference in prevalence of scoliosis between GH-treated versus age-matched GH-untreated children with PWS at 11 years of age. We also found that GH-treated children do not have more severe scoliosis, as the median Cobb angle between the GH-treated and untreated group was similar. Our data show that 8 years of GH treatment

has no adverse effects on the prevalence and severity of scoliosis in children with PWS. Our findings do also show that $BMAD_{LS}$ SDS is inversely associated with Cobb angle, indicating that it is important to optimise BMD-status in children with PWS. Furthermore, the GH-treated children had a taller stature and higher trunkLBM:BSA ratio, which is in line with previous studies showing that GH treatment improves height and lean body mass in children with PWS[34–36].

The prevalence of scoliosis and the median Cobb angle were similar in the GH-treated children and in the age-matched GH-untreated children. The prevalence of a more severe scoliosis (>25º) tended to be lower in the GH-treated group and the GH-treated children were less likely to need surgery or brace therapy than the control group (both 5.8% vs.8.7% resp.), albeit not significantly. These long-term results are in line with our previous study, a randomized controlled trial investigating the effects of 2-year GH treatment on the onset and progression of scoliosis in PWS. During that 2-year study, height velocity and IGF-1 SDS were also not associated with curve progression[14]. In a retrospective study, Nakamura et al. showed similar findings[37]. However, these studies were investigating the effects of short-term GH treatment on scoliosis in PWS, while we know that it takes several years to develop scoliosis and that the prevalence of scoliosis increases when children with PWS become older[8]. Our present findings show that also on the long-term, GH treatment does not affect the prevalence or severity of scoliosis in children with PWS.

Age at start of GH treatment was not associated with Cobb angle after 8 years of GH treatment. A survey from the PWSA found that for every month delay in starting GH treatment, the risk of needing scoliosis surgery increased by 0.7%[15]. Our data do not support this finding. An explanation of this difference could be the fact that children who receive GH are likely to also receive multidisciplinary care from a younger age than children who do not receive GH, including physical therapy, which is also beneficial against development of scoliosis. In addition, almost all children in our GH-treated group started GH at a young age,

which might explain why we were not able to find an age correlation. Due to the positive effects of GH treatment[16–20] and our present findings, we strongly advice to start GH treatment at a young age.

Lower $BMAD_{LS}$ SDS was associated with a higher Cobb angle after 8 years of GH treatment, and there was a trend towards an association between lower BMD_{TB} SDS and higher Cobb angle. A lower BMD was not the result of a vitamin D deficiency, as all vitamin D levels were within the normal range. After 8 years of GH treatment BMD_{TB} SDS was lower in the children with scoliosis compared to those without and the $BMAD_{LS}$ SDS tented to be lower in the children with scoliosis. Nakamura et al did not find a difference in mean BMD between PWS patients with scoliosis and without scoliosis[37], but in the general population, a low BMD is associated with adolescent idiopathic scoliosis (AIS)[38]. Our study shows the importance of BMD-status in relation to scoliosis in children with PWS and we, therefore, advise to optimise BMD-status in children and adolescent with PWS.

After 8 years of GH treatment, we found no difference in height SDS between children who developed scoliosis and those without scoliosis (-0.02 SDS and 0.78 SDS resp.). This finding does not support the current hypothesis that catch-up growth after the start of GH treatment increases the risk of developing scoliosis in children with PWS. It contrasts with findings in AIS, where growth acceleration during puberty has a major influence on the spinal curvature[39,40]. Our data suggest that hypotonia is the main cause of scoliosis in children with PWS and not the catch-up growth after the start of GH treatment. GH-treated children were taller and had higher trunkLBM:BSA ratio, suggesting that a higher lean body mass of the trunk may counteract the effect of the GH-induced accelerated growth on the development of scoliosis in children with PWS.

There was no difference in pubertal stage between the GH-treated children with scoliosis and those without scoliosis. Children treated with GH for 8 years were more likely to have entered

puberty and had a higher Tanner stage than the untreated age-matched controls. We previously found that the prevalence of scoliosis increased with pubertal stage[8,14] Our present results are reassuring, that although the GH-treated children were further into puberty, a similar prevalence and severity of the scoliosis was found as in the untreated children.

Our data showed no difference in prevalence and severity of scoliosis between boys or girls. In the general population, AIS is more frequently seen in girls[41]. Nagai et al. also described a greater risk for developing scoliosis in girls with PWS[22]. In contrast, Kroonen et al. showed that male PWS patients were more at risk of needing treatment for scoliosis[9]. According to the survey by the PWSA, girls were more prone to develop scoliosis, but the progression of the scoliotic curve between the sexes was equal[15]. In our present study, in 103 children with PWS, sex did neither affect the prevalence of scoliosis nor the severity of scoliosis.

There was no significant difference in genetic subtype between the group with and without scoliosis after 8 years of GH treatment and the Cobb angle was not associated with the genetic subtype. The PWSA survey among caregivers of persons with PWS reported that patients with a mUPD appeared to have an increased risk of developing scoliosis, with similar progression of the scoliotic curve between the genetic subtypes[15]. Our findings are in line with other studies reporting that the genetic causes underlying PWS do not influence the frequency and severity of scoliosis[10–12].

Because all Dutch children with PWS are nowadays treated with GH from a young age, we could only include a small number of untreated children in the age-matched control group. An RCT would have been the first-choice design to investigate the long-term effects of GH on scoliosis in children in PWS, but it would be unethical to withhold children with PWS from GH treatment for 8 years. The PWS control group was prior to GH treatment and could, therefore, act as an age-matched untreated control group. As standard PWS care in the

Netherlands includes physical therapy, all children in the control group received physical therapy when the X-rays were made. Therefore, no bias was assumed due to a difference in treatment other than GH treatment. The median BMI SDS was comparable between the GH-treated children and untreated controls, supporting our assumption that there was no bias due to a difference in standard care.

In our Dutch PWS cohort, GH treatment was started at a young age. Our GH-treated group is, therefore, still young after 8 years of GH treatment. Surgery for scoliosis in PWS occurs mostly at an older age[42]. It might be that the prevalence of surgery or brace therapy in our study is an underestimation due to the relatively young age. Further longer-term studies on the effects of GH on scoliosis development and progression in PWS are needed, preferably from the start of GH treatment into adulthood.

In conclusion, this is the first study investigating the long-term effects of GH treatment on the prevalence and severity of scoliosis in children with PWS. Eight years of GH treatment had no adverse effect on the prevalence and the severity of scoliosis in children with PWS. Based on these findings, scoliosis should neither be considered as a contraindication to start GH treatment, nor as a reason to discontinue GH treatment or to lower the GH dosage in children with PWS who develop scoliosis. Because of the high prevalence of scoliosis in PWS, it is recommended to perform X-rays and physical examination on a regular basis. Extra attention for the BMD status of the children with PWS is pivotal, as $BMAD_{LS}$ SDS is inversely associated with Cobb angle. Multidisciplinary care and start of GH treatment at a very young age will optimize the treatment of children with PWS.

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Figure 1. Long C-curve Scoliosis (A) and Idiopathic Scoliosis (B)

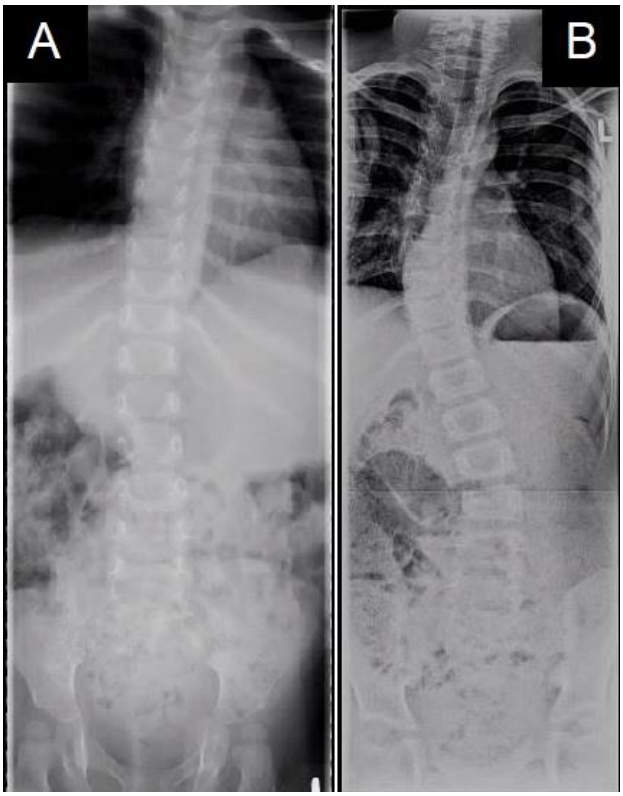

Table 1. Baseline characteristics

	GH treatment group	GH-untreated children	*p*-value
Gender (♂ / ♀)	53 / 50	10 / 13	0.489
Genetic subtype N (%)			0.653
Deletion	51 (49.5%)	9 (39.1%)	
mUPD	42 (40.8%)	9 (39.1%)	
ICD	5 (4.9%)	3 (8.7%)	
At start of GH treatment			
Age (years)	2.8 (1.3; 5.9)	NA	
Height SDS	-2.1 (-2.9; -1.4)	NA	
Weight for height SDS	0.3 (-0.9; 1.5)	NA	
BMI SDS	0.4 (-0.9; 1.4)	NA	
TrunkLBM:BSA	7.2 (6.8; 7.7)	NA	
Cobb Angle (º)	10.3 (7.1; 13.0)	NA	

Data are expressed as median (IQR) or N (%). mUPD: maternal uniparental disomy. ICD: imprinting center defect. GH: growth hormone. BMI: body mass index. TrunkLBM:BSA: Trunk lean body mass / body surface area. NA: not available.

Table 2. Results after 8 years of GH-treatment compared to age-matched untreated controls

	After 8 years of GH (N=103)	GH-untreated children (N= 23)	*p*-value
Age (years)	10.81 (9.27; 13.76)	11.42 (9.7; 13.35)	0.912
Pubertal stage			0.020
Prepubertal / girls	49 (47.6%) / 18	18 (78.3%) / 9	
Early puberal / girls	42 (40.8%) / 23	5 (21.7%) / 4	
Late pubertal / girls	12 (11.7%) / 9	0 (0.0%)	
Height SDS	0.17 (-0.87; 0.94)	-2.60 (-3.46: -1.93)	<0.001
BMD_{TB} SDS	-0.42 (-1.25; 0.58)	-0.74 (-1.35; 0.15)	0.490
BMD_{LS} SDS	0.39 (-0.53; 1.28)	-0.94 (-1.32; -0.07)	0.001
$BMAD_{LS}$ SDS	0.32 (-0.34; 1.14)	0.12 (-0.67; 1.50)	0.768
BMI SDS	1.19 (0.17; 1.85)	1.41 (0.62; 2.17)	0.284
Fat% SDS	1.93 (1.43; 2.38)	1.75 (1.26; 2.17)	0.245
TrunkLBM:BSA	8.83 (8.13; 9.66)	8.16 (7.40; 8.62)	0.001
Serum IGF-1 SDS	2.12 (1.72; 2.53)	-2.41 (-2.97; 1.68)	0.023
Cobb Angle (º)	18.0 (10.5; 30.0)	15.0 (7.5; 32.0)	0.232
Scoliose (%)	80 (77.7%)	16 (69.6%)	0.409
10-24.9º	49 (61.3%)	9 (56.3%)	0.709
>25 º	31 (38.8)	7 (43.8)	0.709
Brace (%)	6 (5.8%)	2 (8.7%)	0.637
Surgery (%)	6 (5.8%)	2 (8.7%)	0.637

Data are expressed as median (IQR) or N (%).
GH: growth hormone. BMD_{TB}: bone mineral density of the total body. $BMAD_{LS}$: bone mineral apperent density of the lumbar spine. BMI: body mass index. TrunkLBM:BSA: Trunk lean body mass / body surface area. Both the surgical and the brace group consisted of 6 individual patients.

Table 3. Scoliosis compared to no scoliosis after 8 years of GH treatment

	Scoliosis (n=80)	No scoliosis (N=23)	*p*-value
Age start GH	2.96 (1.32: 6.12)	2.51 (1.55; 4.56)	0.638
Genotype			0.316
Deletion	42 (52.5%)	9 (39.1%)	
mUPD	29 (36.3%)	13 (56.5%)	
ICD	4 (5.0%)	1 (4.3%)	
Sex (M)	40 (50%)	11 (55%)	0.581
Height SDS	-0.02 (-0.88; 0.69)	0.78 (-0.84; 1.67)	0.051
Pubertal stage			0.513
Prepubertal	40 (50%)	9 (39.1%)	
Early pubertal	32 (40%)	10 (43.5%)	
Late pubertal	8 (10%)	4 (17.4%)	
BMD_{TB} SDS	-0.56 (-1.40; 0.37)	0.14 (-1.01; 1.13)	0.036
BMD_{LS} SDS	0.31 (-0.85; 1.11)	0.88 (-0.01; 1.78)	0.013
$BMAD_{LS}$ SDS	0.28 (-0.56; 1.00)	0.63 (0.16; 1.53)	0.054
BMI SDS	1.15 (0.16; 1.82)	1.61 (0.48; 1.89)	0.343
Fat% SDS	1.88 (1.34; 2.33)	2.16 (1.52; 2.48)	0.141
TrunkLBM:BSA	8.94 (8.11; 9.80)	8.72 (8.30; 9.59)	0.713
Serum IGF-1 SDS	2.13 (1.73; 2.53)	2.08 (1.45; 2.54)	0.692
Serum 25 (OH) vit D* (nmol/l)	63 (50; 88)	67 (43; 73)	0.758

Data are expressed as median (IQR) or N (%).
*GH: growth hormone. BMD: bone mineral density. BMAD: bone mineral apperent density. BMI: body mass index. TrunkLBM:BSA: Trunk lean body mass / body surface area. * normal range 50-120 nmol/l*