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Scoliosis in Prader–Willi syndrome: prevalence, effects of age, gender, body mass index, lean body mass and genotype

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ABSTRACT

Background: The reported prevalence of scoliosis in children with Prader–Willi syndrome varies from 15% to 86%.

Objective: To study the prevalence of scoliosis and the effects of age, gender, body mass index (BMI), total lean body mass (LBM), LBM of the trunk (trunkLBM) and genotype.

Design: Radiographs were taken, length and weight were measured (BMI standard deviation scores (BMI SDS) and body surface area (BSA)), and dual energy x-ray absorptiometry was performed, measuring LBM and trunkLBM.

Patients: 96 children, median (interquartile range) age 4.8 years (2.1 to 7.5), were included in a multicentre study. None received growth hormone treatment.

Main outcome measures: Two types of scoliosis were identified: (1) long C-curve type scoliosis (LCS) and (2) idiopathic scoliosis (IS). Children were divided into age categories (infants, 0–3 years; juveniles, 3–10 years; adolescents, 10–16 years).

Results: The prevalence of scoliosis was 37.5% and increased with age (infants and juveniles, ~30%; adolescents, 80%); 44% of children with scoliosis had a Cobb angle above 20°. Children with scoliosis were significantly older than those without. Children with LCS were younger and more hypotonic than those with IS: median (interquartile range) age 4.4 years (1.7–5.9) vs 11.1 years (6.5–12.1) ($p = 0.002$) and trunkLBM/BSA ratio 7080 (6745–7571) vs 7830 (6932–8157) ($p = 0.043$).

Conclusions: The prevalence of scoliosis in children with Prader–Willi syndrome is high (37.5%). Many children with scoliosis (13%) had undergone brace treatment or surgery. The type of scoliosis is affected by age and trunkLBM/BSA ratio.

Prader–Willi syndrome (PWS) is characterised by hypotonia, hypogonadism, short stature, hyperphagia with obesity, and psychological and behavioural problems.^{1–4}

PWS results from the lack of paternal expression of the q11–q13 region of chromosome 15, caused by deletion, uniparental disomy, imprinting centre defect causing maternal imprinting or balanced translocation.^{5–12} Hypothalamic dysfunction may be responsible for many features of PWS.^{13–15} The birth incidence of PWS is 1:22 000 to 1:29 000. The overall annual death rate under the age of 30 years is 3%.^{16–18}

Children with PWS may develop scoliosis.^{17–22} Scoliosis is a spinal curve with a Cobb angle of

What is already known on this topic

- ▶ The prevalence of scoliosis in patients with Prader–Willi syndrome (PWS) is high (15–86%).
- ▶ Body mass index measured in kg/m² does not affect the risk of developing scoliosis.

What this study adds

- ▶ The prevalence of scoliosis in children with PWS without growth hormone treatment is 37.5%, increasing in adolescence (30% under 10 years, 80% above 10 years).
- ▶ In children with PWS, two types of scoliosis can be distinguished: long C-curve type scoliosis and scoliosis resembling idiopathic scoliosis. There is a strong association between the types of scoliosis and age and the truncal lean body mass/body surface area ratio.
- ▶ The number of children with PWS with moderate or severe scoliosis is alarmingly high.

more than 10° on a standing posteroanterior radiograph. The Cobb angle is the angle between the two steepest vertebrae—that is, the upper border of the upper vertebra in the curve and the lower border of the lower vertebra.²³

Information on scoliosis in PWS is limited and varies greatly. The prevalence of scoliosis in children with PWS has been estimated to be 15–86%.^{17–22} All studies were retrospective and included both adults and children, without and during growth hormone treatment.^{17–21} Some calculated prevalences from questionnaires, whereas others studied material assembled over a large time span.^{17–22}

We conducted a multicentre study to investigate the prevalence and severity of scoliosis in a large group of children with PWS without growth hormone treatment and studied the effects of age, gender, body mass index (BMI), lean body mass (LBM) and genotype on scoliosis.

METHODS

Patients

Patients were included from April 2002 until November 2006. Ninety-six children with PWS

(table 1) were recruited through their paediatricians and paediatric endocrinologists for a national study and fulfilled the following inclusion criteria: (1) genetically confirmed diagnosis of PWS by positive methylation test; (2) age between 6 months and 16 years; (3) bone age less than 14 years (girls) or 16 years (boys). None of the children were treated with growth hormone. All children visited the Erasmus Medical Centre/Sophia Children's Hospital in Rotterdam, The Netherlands.

The study protocol was approved by the medical ethics committee of ErasmusMC, Rotterdam, The Netherlands. Informed consent was obtained from parents and children above 12 years.

Radiographics

Standing posteroanterior radiographs were taken of children who were able to stand. In young and/or hypotonic children who were not able to stand, posteroanterior radiographs in the supine position were taken. Cobb angles were measured by two observers, a clinical research fellow (RdL) and an experienced paediatric orthopaedic surgeon (LdK). A triage system was used: one observer (RdL) measured all spinal radiographs, the other observer (LdK) examined all scoliotic curves. Intraobserver variation (RdL: mean (SD) difference -0.05 (1.78) $^{\circ}$, intraclass coefficient (ICC) = 0.998, $\rho = 0.994$, $p = 0.01$, 95% CI = -0.91 to 0.80) and interobserver variation (mean (SD) difference -0.02 (3.1) $^{\circ}$, $\rho = 0.94$, ICC = 0.97, $p = 0.01$, 95% CI = -0.89 to 0.85) were minimal. Consistency between conventional and digital measurements was very high (mean (SD) difference 0.03 (1.54) $^{\circ}$, $\rho = 0.969$, ICC = 0.98, $p = 0.01$, 95% CI = -0.52 to 0.59).

A thoracic scoliosis was defined as a scoliosis with its apex between the second and 11th thoracic vertebra. A thoracolumbar scoliosis has its apex at either the 12th thoracic or first lumbar vertebra. The apex is the most displaced vertebra in the scoliotic curve.

Two types of scoliosis were identified: (1) long C-curve type scoliosis, often seen in children with neuromuscular disorders (LCS); (2) scoliosis behaving much like idiopathic scoliosis and which could therefore be classified according to the Lenke classification system (IS) (figs 1 and 2).²⁴

Anthropometrics

Supine length was recorded below the age of 2.5 years. Thereafter, standing height was measured with a Harpenden stadiometer. Weight was assessed on an accurate scale, and BMI (kg/m^2) was calculated. Height and BMI were converted into standard deviation score (SDS) according to Dutch references for age.^{25 26} Body surface area (BSA) was calculated. Calculations were performed with Growth Analyser V3.0 (www.growthanalyser.org).

Dual-energy x-ray absorptiometry (DXA)

Lean body mass (LBM) was measured by DXA (Lunar Prodigy; GE Healthcare, Chalfont St Giles, UK). As no reference values for LBM in very young children were available, an LBM/BSA ratio was used for total LBM calculations and a trunkLBM/BSA ratio for calculations using only the LBM of the trunk. TrunkLBM, a measure of central LBM, is the total LBM in the chest, abdomen and pelvis.

Data analysis

Data were analysed for all children and for different age categories: infantile (0–3 years), juvenile (3–10 years) and adolescent (10–18 years) scoliosis.^{27 28} Statistical analysis was performed with SPSS V11.0. Most of the data obtained in our patients were not Gaussian distributed. We therefore expressed our data as median and interquartile range (iqr). Non-parametric tests (Mann–Whitney U test) and χ^2 tests were used to compare results between different age categories and types of scoliosis. Correlations were calculated using Spearman's correlation coefficient (r).

RESULTS

Ninety-six children were included in this study (table 1). Median (iqr) age was 4.8 years (2.1–7.5) and BMI SDS was 1.1 (-0.2 to 1.9). Height SDS was significantly different between the infant and juvenile group ($p = 0.02$) and between the juvenile and adolescent group ($p = 0.002$). Weight SDS was significantly different between all groups (infant and juvenile $p < 0.0001$, infant and adolescent $p < 0.0001$, juvenile and adolescent $p = 0.002$). The detailed genotype of 82 children was known: 38 had a deletion (46%), 35 uniparental disomy

Table 1 Overview of the study population and the prevalence and severity of scoliosis

	Total	Infants	Juveniles	Adolescents
Age range (years)	0.5–16	0–3	3–10	10–16
Number (m/f)	96 (52/44)	30 (24/6)	51 (20/31)	15 (8/7)
Age (years)	4.8 (2.1 to 7.5)	1.6 (1.2 to 2.0)	5.8 (3.9 to 7.0)	11.9 (11.5 to 14.8)
Height SDS	-2.3 (-3.1 to -1.4)	-1.5 (-2.6 to -0.7)	-2.5 (-3.2 to -1.8)	-2.2 (-3.8 to -1.8)
Weight SDS	1.2 (-0.4 to 2.0)	-0.9 (-1.7 to 1.2)	1.3 (0.3 to 1.9)	2.2 (1.9 to 3.3)
TrunkLBM/BSA ($\times 10^{-3}$)	7.3 (6.8 to 7.8)	6.9 (6.6 to 7.6)	7.3 (6.9 to 7.7)	8.1 (7.8 to 8.4)
Scoliosis	36 (38)	9 (30)	15 (29)	12 (80)
LCS	13 (36)	6 (67)	7 (47)	0
IS	23 (64)	3 (33)	8 (53)	12 (100)
10–19 $^{\circ}$	18 (19)	7 (23)	9 (18)	2 (13)
20–39 $^{\circ}$	6 (6)	2 (7)	1 (2)	3 (20)
Brace	4 (4)	0	2 (4)	2 (13)
Surgery	8 (8)	0	3 (6)	5 (33)

Overview of the total number of children, the median (interquartile range) age, height SDS, weight SDS and trunkLBM/BSA ratio of children included in the study. Also, the number (%) of children with scoliosis according to type of scoliosis, the Cobb angles and the number (%) of children treated for scoliosis are stated. BSA, body surface area; IS, idiopathic scoliosis; LBM, lean body mass; LCS, long C-curve type scoliosis; SDS, standard deviation score.

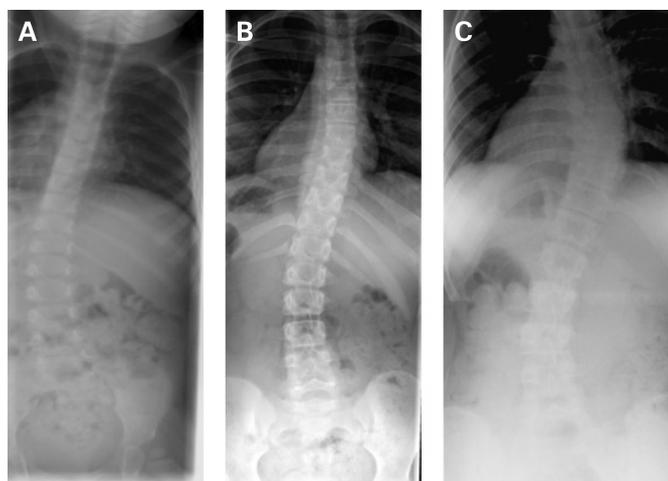


Figure 1 Examples of long C-curve type scoliosis (A) and scoliosis resembling idiopathic scoliosis (B, C).

(43%), eight imprinting centre defect (10%), and one a balanced chromosomal translocation (1%).

Scoliosis in the total group of children with PWS

Of 96 children, 36 had scoliosis (21 boys, 15 girls) at a median (iqr) age of 6.9 years (3.0–11.5). The total prevalence of scoliosis in our group of children with PWS was 37.5% (table 1). The prevalence was much higher than in the Dutch non-PWS population (scoliosis 2.7%; 10–19°, 2%; 20–39°, 0.5%).²⁹ Thirteen cases of scoliosis (36%) were classified as LCS, and 23 (64%) as IS.

The median (iqr) Cobb angle of all cases of scoliosis was 18.3° (12.9–35.0). Eighteen children (50% of all with scoliosis; table 1) had Cobb angles of 20° and more, the severity of scoliosis for which children are generally referred to an orthopaedic surgeon. Twelve children (13%) had undergone conventional (Boston brace) or surgical treatment.

There was no difference in the number of children with thoracic and thoracolumbar scoliosis between those with IS and those with LCS.

Lenke classification of 15 children with IS indicated that most of them (7 children, 47%) had type 1B scoliosis (fig 2), in which the main curve is thoracic and the centre sacral vertical line is out of alignment, just touching the apical bodies.²⁴

There was no difference in prevalence, severity, location of the apex or Lenke classification between boys and girls and between different genotypes. Compared with boys, girls showed more IS than LCS. This difference, however, did not reach significance ($p=0.089$), possibly because of the small numbers.

We did not find any congenital spinal anomalies, which is in line with the results of Kroonen *et al.*²⁰

Infantile scoliosis

Nine of 30 infants with PWS (30%) had scoliosis (table 1). Six children had LCS (67%), and three had IS (33%). Two children had thoracic scoliosis and seven had thoracolumbar scoliosis. The median (iqr) Cobb angle of all infantile scoliosis was 15.5° (13.3–21.5). Two children had Cobb angles greater than 20° and were therefore monitored by an orthopaedic surgeon. At the time of measurement, none of them yet needed treatment (table 1).

Lumbar spine modifier	Curve type (1–6)					
	Type 1 (main thoracic)	Type 2 (double thoracic)	Type 3 (double major)	Type 4 (triple major)	Type 5 (TL/L)	Type 6 (TL/L-MT)
A (No to minimal curve)	1A*	2A*	3A*	4A*		
B (Moderate curve)	1B*	2B*	3B*	4B*		
C (Large curve)	1C*	2C*	3C*	4C*	5C*	6C*
Possible sagittal structural criteria (to determine specific curve type)	Normal	PT kyphosis	TL kyphosis	PT + TL kyphosis		

*T5–12 sagittal alignment modifier: -, N, or +
 -: < 10°
 N: 10–40°
 +: > 40°

Figure 2 Lenke classification system for idiopathic scoliosis. Reprinted with permission from *The Journal of Bone and Joint Surgery*. Most children had type 1B scoliosis.

Juvenile scoliosis

Of 51 children aged 3–10 years, 15 had juvenile scoliosis (29%). Seven had LCS (47%), and eight had IS (53%). Four children had thoracic scoliosis, and eight had thoracolumbar scoliosis. The median (iqr) Cobb angle of all juvenile scoliosis was 14.5° (12.5–35.0). Six children had Cobb angles greater than 20°. Five of them (10% of children with juvenile scoliosis) were treated, and one was still being monitored (table 1).

Adolescent scoliosis

The prevalence of scoliosis in children 10 years and older was 80%. Cases of adolescent scoliosis were all classified as IS (Table 1). The median (iqr) Cobb angle of all adolescent scoliosis was 35.0° (19.0–41.5). Ten children had Cobb angles greater than 20°. Seven children (47% of children with adolescent scoliosis) were treated, and two were still being monitored (table 1).

Effects of age

Children with scoliosis were significantly older than those without scoliosis ($p=0.007$; table 2). Adolescent children showed significantly more scoliosis than infant and juvenile children with PWS ($p=0.002$ and $p=0.0001$, respectively). There was no significant difference in the number of children with scoliosis between the infant and juvenile group ($p=0.96$).

Table 2 Differences between children with Prader–Willi syndrome with and without scoliosis

	No scoliosis	Scoliosis	LCS	IS
Age (years)*	3.7 (1.9–6.5)	6.9 (3.0–11.5)	4.4 (1.7–5.9)	11.1 (6.5–12.1)
BMI (SDS)†	0.6 (–0.2 to 1.7)	1.3 (–0.4 to 2.4)	1.1 (–0.8 to 1.5)	1.9 (1.0 to 2.6)
LBM/BSA ($\times 10^{-4}$)	1.5 (1.5–1.6)	1.6 (1.5–1.7)	1.6 (1.5–1.6)	1.6 (1.5–1.7)
TrunkLBM/BSA ($\times 10^{-3}$)‡	7.3 (6.8–7.8)	7.5 (6.9–7.9)	7.1 (6.7–7.6)	7.8 (6.9–8.2)

Differences in age, BMI SDS, LBM/BSA and trunkLBM/BSA for children with and without scoliosis, also according to type of scoliosis. Values are expressed as median (iqr).

*Children with scoliosis were older than those without ($p = 0.007$) and children with LCS were younger than those with IS ($p = 0.002$).

†Children with scoliosis had a higher BMI SDS than those without ($p = 0.05$). Children with IS had a higher BMI SDS than children with IS ($p = 0.026$).

‡Children with LCS had a significantly lower LBM/BSA than children with IS ($p = 0.043$).

BMI, body mass index; BSA, body surface area; IS, idiopathic scoliosis; LBM, lean body mass; LCS, long C-curve type scoliosis; SDS, standard deviation score.

Children with LCS were significantly younger than children with IS ($p = 0.002$; table 2). Adolescent children showed significantly more IS than infant and juvenile children with PWS ($p = 0.001$ and $p = 0.006$, respectively). There was no significant difference in type of scoliosis (LCS or IS) between the infant and juvenile group ($p = 0.34$).

A higher percentage of children was treated in the adolescent group than in the infantile and juvenile group ($p = 0.0001$ and $p = 0.001$, respectively; table 1). This difference did not reach significance between the infantile and juvenile group, probably because of small numbers ($p = 0.077$). Our data indicate that scoliosis in children with PWS is progressive with age.

The difference in location of the apex between infants (mainly thoracolumbar scoliosis) and adolescents (mainly thoracic scoliosis) was significant ($p = 0.036$).

BMI and LBM

TrunkLBM/BSA was significantly different between infants and adolescents ($p < 0.0001$) and between the juvenile and adolescent group ($p < 0.0001$; table 1). BMI SDS and trunkLBM/BSA correlated significantly with age ($r = 0.40$ with $p = 0.01$ and $r = 0.54$ with $p = 0.01$, respectively).

Children with scoliosis had a significantly higher BMI SDS than children without scoliosis ($p = 0.05$; table 2). Children with LCS had significantly lower BMI SDS and trunkLBM/BSA than those with IS ($p = 0.026$ and $p = 0.043$, respectively).

DISCUSSION

Our study shows a prevalence of scoliosis in patients with PWS of 37.5%, increasing in adolescence (30% in infants, 29% in juveniles and 80% in adolescents). Fifty percent of children with scoliosis had Cobb angles greater than 20° , and 13% of them were treated. Our data show that scoliosis is a progressive deformity and therefore the percentage of treated scoliosis increased with age. Children with scoliosis were older with higher BMI SDS than those without.

We identified two types of scoliosis: LCS and IS. Girls were more likely to have IS than LCS compared with boys, but this difference did not reach statistical significance. More importantly, infants mainly showed LCS, whereas adolescents only showed IS; juvenile children showed both types of scoliosis. This may indicate a shift in a single patient from an LCS-type to an IS-type scoliosis, or a transition as a total group evolving from regression of LCS and new development of IS. The LCS-type scoliosis showed a strong association with a low trunkLBM/BSA, used as a proxy for hypotonia of the trunk. The decreasing number with LCS-type scoliosis with age in

children with PWS may therefore be associated with an increase in trunkLBM. This is an interesting matter for future research.

The prevalence of scoliosis of 37.5% is much higher than in the non-PWS Dutch population (2.7%).²⁹ Importantly, our study also shows a very high prevalence of both infantile and juvenile scoliosis (~30%). Interestingly, Nagai *et al*²¹ reported a prevalence of 25% in patients aged 6–11 years. This study also reported that girls were at greater risk of developing scoliosis,²¹ whereas Kroonen *et al*²⁰ treated more male patients. As could be expected from these results, gender did not affect the prevalence of scoliosis in our study. This is in contrast with the Dutch non-PWS population, in which the male/female ratio is 1:1.2.²⁹

Owing to the high prevalence of scoliosis, it is advisable to perform frequent physical examinations of the spine (Adam's forward bend test) in children with PWS during routine visits. However, physical examination may not be reliable for detecting scoliosis in children with obesity and/or hypotonia. In such children and in those with suspected scoliosis, yearly radiographic examination (preferably standing posteroanterior radiographs) is advisable. We recommend that all patients with PWS with scoliosis of 20° or more be referred to an orthopaedic surgeon. In our clinic, non-PWS children with progressive scoliosis of 20 – 25° or more are treated with a Boston brace. In children with PWS, however, the efficacy of the bracing is very limited because of hypotonia and obesity. Furthermore, if effective, psychological problems (eg, temper tantrums) may complicate compliance. Children with progressive scoliosis despite bracing, or with scoliosis of 45° or more, are candidates for spinal surgery. Surgery may be high-risk and contraindicated in some patients with PWS. However, severe progressive scoliosis may become a life-threatening deformity in itself. In short, the choice of treatment is complicated, and the potential result should be weighed against possible complications.

Increased growth velocity during puberty and catch-up growth initiated by growth hormone treatment have caused development or progression of scoliosis in non-PWS patients prone to developing scoliosis.^{30–32} Because many patients with PWS have reduced growth velocity, they are often treated with growth hormone. It would be interesting to perform a longitudinal study on the effects of growth and growth hormone treatment on the development or progression of scoliosis.

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Patient consent: Obtained/parental consent obtained.

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