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ARTICLE

Scoliosis in Patients With Prader-Willi Syndrome

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What's Known on This Subject

Scoliosis frequency in patients with PWS has been reported already, but we do not yet have published data to provide a detailed analysis of risk factors such as genotype, BMI, or GH treatment in a large cohort of patients.

What This Study Adds

This study adds a response on risk-factor analysis for scoliosis onset and progression. We found a correlation of kyphotic deformity associated with scoliotic deformity and the need for surgical treatment.

ABSTRACT

OBJECTIVE. Our goals were to determine the prevalence and estimate the evolution of spinal deformities in patients suffering from Prader-Willi syndrome; find out which kind of spine deformity predominates regarding genotype and clinical patterns; and evaluate the affect of growth-hormone treatment on the onset and progression of spinal deformities.

PATIENTS AND METHODS. This was a retrospective longitudinal, clinical, and radiologic study. One hundred forty-five children followed between 1980 and 2006 were studied in 2 referral centers for Prader-Willi syndrome. Genetic testing confirmed the diagnosis in 133 patients. Ninety-three patients (64%) received growth-hormone therapy. For statistical analysis, age-adjusted comparison between groups was performed by using multivariate logistic regression.

RESULTS. Mean age of the patients was 10.2 ± 6.2 years. Sixty-three (43.4%) patients were afflicted with scoliosis. Scoliosis frequency steadily rose with age, and a large majority of patients were affected at skeletal maturity (66.7%). Scoliosis prevalence was not affected by the genotype or by growth-hormone treatment. Patients with higher BMI values had an increased risk of developing a kyphotic deformity in association with scoliosis. We found a statistical association between kyphotic deformity and the need for surgical treatment.

CONCLUSIONS. Scoliosis is a major concern for patients with Prader-Willi syndrome, and a regular (annual) systematic back examination is mandated. The role of growth-hormone treatment on the natural history of scoliosis could not be determined, and careful monitoring during treatment is recommended. *Pediatrics* 2008;122:e000

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Key Words
growth and nutrition, growth-hormone treatment, Prader-Willi syndrome, scoliosis

Abbreviations
PWS—Prader-Willi syndrome
GH—growth hormone
IQR—interquartile range
SG—scoliosis group
NSG—nonscoliosis group

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PRADER-WILLI SYNDROME (PWS) is the most frequent cause of syndromic obesity and occurs in 1 in 25 000 live births. The syndrome was first described in 1956 as the Prader-Labhart-Willi syndrome,[1] characterized by neonatal hypotonia and failure to thrive during the first months of life followed by severe hyperphagia, morbid obesity, and other associated signs such as short stature, dysmorphic features, learning difficulties, and behavioral and psychiatric problems. The consensus criteria for diagnosis were first established by Holm et al[2] and subsequently simplified according to the age of the patient.[3] Early diagnosis and multidisciplinary care involving growth-hormone (GH) treatment have been shown to have a role in management of the condition in these children, particularly in reducing the incidence of obesity.[4–6]

Most cases arise sporadically. PWS often results from loss of the paternal copy of chromosome 15 q11-q13. More than 70% of patients have a deletion of the paternal copy, and ~25% of patients have a maternal uniparental disomy of chromosome 15. The remaining patients have a translocation or another structural alteration in chromosome 15.[7,8]

Scoliotic and kyphotic deformities were included as supportive features in the consensus criteria established by Holm et al.[2] With improvement in the care of these patients, spinal deformity is diagnosed more frequently and has arisen to the forefront. An increased prevalence of scoliosis in patients with PWS was first reported by Gurd and Thompson,[9] and a prevalence of 41% to 80% has been reported.[2–11] GH therapy has been administered to patients

TABLE 1 **Variables Distribution in Accordance With Scoliosis**

	SG ($n = 63$)	NSG ($n = 82$)	P	P^a
Mean age at follow-up ± SD, y	12.9 ± 5.6	8.1 ± 5.5	<.001	—
Male gender, *n* (%)	28 (44.4)	43 (52.4)	.34	.54
Genotype ($N = 133$), *n* (%)			.62	.61
Deletion	40 (74.1)	50 (63.3)	—	—
Disomy	12 (22.2)	24 (30.4)	—	—
Abnormal methylation profile	2 (3.7)	5 (6.3)	—	—
BMI *z* score ($N = 144$), median (IQR)	3.28 (0.7–5.8)	1.78 (0.2–4.3)	.07	.45
Walking age ($N = 114$), median (IQR), mo	25 (21–36)	24 (20–30)	.12	.19
GH treatment, *n* (%)	38 (60.3)	55 (67.1)	.74	.26

[a] Adjusted for age.

with PWS with satisfactory results in terms of BMI control, improvement of lean body mass, and increased height. As in patients without PWS, the role of GH therapy on scoliosis onset and progression is still debated.[12]

To the best of our knowledge, there have been no published data concerning the affect of risk factors such as genotype, BMI, and hypotonia and GH treatment on the onset, progression, and severity of spinal deformities with PWS. On the basis of a large cohort of children regularly assessed in our referral centers for PWS and spinal deformity, we report here a detailed analysis of risk factors for scoliosis onset and progression.

PATIENTS AND METHODS

We studied 145 consecutive children followed in our 2 institutions (Necker-Enfants-Malades and Toulouse hospitals) for PWS between 1980 and 2006. Demographics, genetic testing analysis and diagnosis, past medical and surgical history, description of clinical behaviors, and GH treatment were recorded. All patients were reviewed systematically at regular intervals between January 1980 and December 2006 by 2 seniors authors (Drs Odent and Sales de Gauzy). Age, gender, height, weight, BMI, and standing spinal coronal and sagittal alignment were assessed. The findings of the Adams Forward Bend test were recorded also. BMI was reported in SDs from the mean BMI (*z* score), which varies with age. We chose the walking age as a marker of patient hypotonia and severity of developmental delay.

Standing anteroposterior and lateral spinal radiographs were obtained routinely during serial follow-up. All spine radiographs obtained in the course of routine clinical care were evaluated. Spinal anteroposterior and lateral radiographs were systematically obtained in the case of abnormal results of the Adams Forward Bend test and every 6 months in GH-treated patients. Curve type was analyzed according to the Scoliosis Research Society classification (a scoliosis was considered in case of a Cobb angle of >10° with a vertebral rotation), whereas the degree of deformity was assessed with Cobb angles. On the lateral radiographs, a kyphotic deformity was defined as an angle of >40° between the T3 and T9 vertebrae in the thoracic area and >10° between L1 and L5 in the lumbar area. A progressive curve was defined as an increase in Cobb angle of >5° within 6 months. Bracing was indicated in case of curve progression. Surgery was performed in case of spinal coronal and/or sagittal imbalance associated with a Cobb angle >50°.

The study group included 64 (44%) female and 71 (66%) male patients with an average age of 10.2 ± 6.2 years. The diagnosis of PWS was genetically confirmed in 133 patients. In the oldest patients, PWS was diagnosed on medical criteria alone. The genetic analysis revealed a deletion in 90 (62%) patients, a uniparental disomy in 36 (25%) patients, and an abnormal methylation profile in 7 (4%) patients. Ninety-three (64%) patients had received GH therapy at a dose of 0.035 mg/kg per day (without exceeding 2.7 mg/day) 6 or 7 days per week.

Data are expressed as mean ± SD. When continuous variables did not display normal distribution, the median and interquartile range (IQR) were reported. The Pearson χ^2 test or Fisher's exact test was used for comparing proportions. One-way analysis of variance or the Mann-Whitney test was used for comparison of means. Age-adjusted comparisons between groups were performed by using multivariate logistic regressions. Data were analyzed by using Stata 9.0 statistical software (Stata Corp, College Station, TX).

RESULTS

Scoliosis Prevalence

Among the 145 patients, 63 (43.4%) had scoliosis (scoliosis group [SG]) and 82 were scoliosis free (nonscoliosis group [NSG]) (Table 1). The main curve was thoracic in 18 cases, thoracolumbar in 19 cases, and lumbar in 8 cases. Eighteen patients had a double curve. Mean age of the patients at follow-up was 12.9 ± 5.6 years in the SG and 8.1 ± 5.5 years in the NSG ($P < .01$). The prevalence of scoliosis according to the 3 age groups was 7 (19.5%) of 36 patients aged 0 to <5 years, 12 (27.9%) of 43 patients aged 5 to 10 years, and 44 (66.7%) of 66 patients aged >10 years ($P < .001$). No influence of gender was noted, with 28 (44%) of 63 male patients in the SG versus 43 (52.4%) of 82 in the NSG ($P = .34$). There was a high proportion of patients with deletion mutations in the SG (74% vs 63% in the NSG; $P = .62$). The median BMI expressed as a *z* score was 3.28 (IQR: 0.7–5.8) in the SG and 1.78 (IQR: 0.2–4.3) in the NSG, with no statically significant difference after adjustment for age at follow-up ($P = .45$). No difference was seen regarding walking age between the 2 groups ($P = .19$).

TABLE 2 **Comparison of Scoliosis Management**

	Observation ($n = 23$)	Brace ($n = 24$)	Surgery ($n = 16$)	*P*, Treatment (Brace ± Surgery) vs Observation	*P*, Surgery vs Other Treatment
Mean age at follow-up ± SD, y	11.2 ± 7.3	12.6 ± 4.3	15.9 ± 3.2	—	—
Male gender, *n* (%)	9 (39.1)	15 (62.5)	4 (25.0)	.37	.10
Genotype ($N = 54$), *n* (%)					
Deletion	16 (72.7)	15 (68.2)	9 (90.0)	—	—
Disomy	6 (27.3)	6 (27.3)	0 (0.0)	—	—
Abnormal methylation profile	0 (0.0)	1 (4.5)	1 (10.0)	—	—
BMI *z* score, median (IQR)	3.1 (0.2–7.5)	1.3 (0.2–4.6)	5.6 (2.8–6.8)	.66	.34
Walking age ($N = 47$), median (IQR), mo	24 (21–31)	24 (20–36)	28 (25–36)	.53	.88
GH treatment ($N = 59$), *n* (%)	15 (65.2)	18 (75)	5 (31.2)	.65	.12
Presence of kyphosis, *n* (%)	4 (17.4)	5 (20.8)	9 (56.3)	.27	.02

All comparisons were adjusted for age.

Of the 93 patients who received GH therapy, 38 (40.9%) developed scoliosis versus 21 (43.7%) of those who did not receive GH therapy. No difference was observed after age adjustment ($P = .26$).

Risks Factors for Scoliosis Progression

Of the 63 scoliotic patients, 23 (36.5%) patients with a mean age of 11.2 ± 7.3 years had a nonprogressive curve and were observed (Table 2). Twenty-four patients had a progressive curve with a Cobb angle of the main curve >15°, which required bracing. The mean curve angle was 31° ± 11°. The mean age of these patients was 12.6 ± 4.3 years. They were braced with either a Milwaukee brace or thoracolumbosacral orthosis depending on their age and type of scoliotic deformity. Sixteen patients had curve progression despite bracing and required surgical treatment. No significant statistical correlation was observed between scoliosis evolution and genotype, BMI, walking age, or GH treatment.

GH was administered to 15 of 24 patients with nonprogressive curves, 18 of 24 braced patients, and 5 of 16 surgically treated patients. The risk of scoliosis progression was not increased in GH-treated patients ($P = .65$). Twenty-three patients had a kyphotic deformity associated with scoliosis. Kyphosis was thoracic in 18 cases and thoracolumbar in 5 cases. We found a statistical correlation between kyphoscoliosis and high BMI values ($P = .007$ after adjustment for age) (Table 3).

Finally, 16 (25.4%) scoliotic patients with a mean Cobb angle of 50° ± 30° and a trunk imbalance received surgery at a mean age of 15.9 ± 3.2 years. All patients treated surgically had a kyphotic component to their deformity. There was a statistical association between kyphotic deformity and the need for surgical treatment ($P = .02$). We also found a correlation between the need for surgical treatment and previous or ongoing GH treatment ($P = .02$), but this difference was not significant after adjustment for age ($P = .12$).

DISCUSSION

Scoliosis deformity has long been underestimated in PWS. With the improvement in early diagnosis and multidisciplinary care, problems such as scoliosis become a concern. The overall frequency ranges from 41% to 80% in the different studies reported. Likewise, our study revealed an important scoliosis prevalence of 70% at skeletal maturity. The prevalence increases with age. We demonstrated an increase in prevalence of 10% every 5 years, until age 10, and observed a flare-up during adolescence, with a large proportion of patients being affected at maturity. As a consequence, screening must be performed on a regular basis. We recommend systematic clinical examination for scoliosis every year.

An overall high frequency of scoliosis is well recognized, but few data are available on risk factors for scoliosis onset and progression. The role of hypotonia of the paravertebral muscles, obesity, bone dysplasia, and

TABLE 3 **Variable Distributions in Accordance With Kyphosis**

	Kyphosis ($n = 23$)	No Kyphosis ($n = 122$)	*P*	*P*[a]
Mean age at follow-up ± SD, y	15.1 ± 6.5	9.3 ± 5.5	<.001	—
Male gender, *n* (%)	12 (52.2)	59 (48.4)	.73	.45
Genotype ($N = 133$), *n* (%)			.27	.26
Deletion	9 (64.3)	81 (68.1)	—	—
Disomy	3 (21.4)	33 (27.7)	—	—
Abnormal methylation profile	2 (14.3)	5 (4.2)	—	—
BMI *z* score ($N = 144$), median (IQR)	5.6 (3.9–7.7)	1.8 (0.2–4.2)	<.001	.007
Walking age ($N = 114$), median (IQR), mo	27 (24–38)	24 (20–30)	.14	.53
GH treatment, *n* (%)	9 (39.1)	84 (68.9)	.03	.39

[a] Adjusted for age.

GH treatment is still debated. We analyzed features that could be postulated to be risk factors. There was no effect of gender or genotype (deletion versus disomy) in our study, these criteria affecting the severity of the phenotype and the risk of scoliosis in the standard population. We did not find any correlation between walking age and development of scoliosis. However, mean walking age was higher in the kyphotic group (24 vs 27 months), and hypotonia may lead to the development of kyphosis.

In the current series, the condition of 40 of the 63 scoliotic patients deteriorated and required treatment with bracing (24) or surgery (16). The control of weight gain is of utmost importance with PWS. Adequate diet and establishing appropriate eating and exercise habits should be primary considerations for caregivers and parents. It was observed in this study that BMI increased in a linear fashion with age. The BMI *z* score was 3.28 in the SG and 1.78 in the NSG, with no statistical significance when adjusted for age. As has been reported by Holm et al,[2] isolated kyphotic deformity is a rare condition in children and adolescents with PWS. In our study we did not find any patient with isolated thoracic kyphosis. In our series, 24 scoliotic patients had an associated thoracic kyphosis, and all of the 16 patients who underwent surgery had a kyphotic component to their deformity. We found a statistical correlation between kyphotic deformity and increased BMI. Kyphoscoliosis leads to curve progression and trunk imbalance in most cases (16 of our 24 patients), which makes surgical intervention necessary.

Many authors have expressed concerns about complications of PWS scoliosis surgery, such as spinal cord injury, postoperative respiratory problems, wound infections, and secondary cervicothoracic collapse above the fused spinal area.[13–15] As a consequence, controlling weight gain is of great importance in scoliotic patients with PWS. It is essential to control the progression of BMI during childhood and adolescence to minimize the risk of developing an associated kyphotic deformity in scoliotic patients.

GH therapy corrects osteopenia and improves lean body mass, physical strength, and agility. On the other hand, GH therapy strongly increases growth velocity and patients with PWS are very sensitive to GH,[16] which could have an affect on scoliosis onset and progression. Docquier et al[17] reported that GH may increase the risk of progression of scoliosis and, furthermore, that this progression is frequently rapid. Thus, decision-making for starting or stopping GH treatment is difficult for physicians of patients with preexisting scoliosis or when scoliosis develops during GH treatment. As already reported,[12] our results demonstrate that the prevalence of scoliosis was not statistically different at any age between patients who received GH and those who did not: 64.4% of patients in the SG and 67.1% of patients in the NSG received GH therapy ($P = .26$). GH therapy induces rapid height gain,[4,5] which would be expected to increase the risk of curve progression. Rapid and substantial curve progression was observed during the first months of GH administration in isolated cases, but no statistical correlation was observed. The risk of curve progression was higher for young patients treated with GH (46%), but the number of patients without GH therapy was too small to draw conclusions. Curve severity was affected by GH treatment, with a correlation observed between previous or ongoing GH treatment and surgical treatment. However, surgical treatment was performed at a mean age of 16 years, and only these older patients who developed the most severe spinal deformities had received GH. In routine practice, GH treatment requires a clinical and radiographic examination before starting and 6 months of stringent monitoring, particularly at puberty. GH therapy has multiple benefits for children with PWS: better BMI control, increased vertical height, and improved socialization. As a consequence, we do not consider GH to be contraindicated for patients with preexisting scoliosis. We have frequently observed scoliosis progression during the first months of GH treatment, but the effect on long-term natural history has not been demonstrated. Only a prospective study, which is currently in progress, would answer this question.

CONCLUSIONS

Although retrospective, our study has revealed a high prevalence of spinal deformity in PWS. The frequency rose steadily with age, and a majority of the patients were affected at skeletal maturity. Scoliosis prevalence was not affected by the genotype or GH treatment. However, patients with higher BMI values had an increased risk of developing a kyphotic deformity in association with their scoliosis. The role of GH therapy in the progression of scoliosis is yet to be established. Nevertheless, we recommend careful monitoring for these patients.

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