Growth hormone supplement treatment reduces the surgical risk for Prader–Willi Syndrome patients

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Received: 20 August 2010 / Revised: 23 March 2011 / Accepted: 4 December 2011 / Published online: 23 December 2011
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Abstract

Introduction Many complications have been reported to occur with surgery for scoliosis in Prader–Willi Syndrome (PWS). However, growth hormone (GH) treatment has contributed to improvements in height, body composition, bone density and breathing functions in PWS patients. The purpose of this study was to investigate patients who underwent surgery for scoliosis in PWS.

Materials There were 136 PWS patients being followed-up by the Pediatrics Department of our hospital. Among these, we investigated nine patients who had undergone surgery. Their mean age was 11 years. The mean follow-up period was 6 years 10 months.

Results The mean body mass index was 22.5 kg/m². GH therapy was administered to eight patients. Brace treatment was performed in two patients. Spinal correction and fusion were performed in six patients, and the growing rod method was performed in three patients. Necessary reoperations were performed in two patients. For the total 11 surgeries in the nine patients, the mean blood loss was

397 ml and the mean operation time was 4 h and 20 min. The mean Cobb angles were 76.0 degrees preoperatively and 35.8 degrees at follow-up. Regarding complications, one patient experienced early dislodgment of the hook and one patient experienced a superior wound infection.

Conclusion There were no severe complications such as deep infections or neurovascular damage. A few obese patients underwent surgery, but there were no dangerous complications. Overall, we consider that GH treatment before surgery may reduce postoperative complications. The growing rod method was effective for PWS patients who resisted brace treatment owing to mental retardation.

Keywords Prader–Willi syndrome · Scoliosis · Surgery · Growth hormone · Growing rod

Background

Prader–Willi Syndrome (PWS) is caused by abnormalities of chromosome 15 and is characterized by weakness of muscle tension, imperfect function of the hypothalamus and pituitary gland, hypogonadism, overeating and obesity. Its orthopedic characteristics include scoliosis, hip dysplasia and lower limb alignment abnormalities. In addition, bone fractures caused by osteoporosis are problematic. Although the prevalence of scoliosis in PWS is 15–86% [1], the prevalence of PWS itself is rare, with only one person per 10,000–20,000 people affected.

Many complications have been reported to occur in surgery for severe scoliosis in PWS [2]. The problems associated with surgery for the treatment of scoliosis in PWS are severe obesity, short height, osteoporosis, sleep apnea, breathing restriction by an obstacle, mental retardation, character action abnormalities and diabetes.

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Growth hormone (GH) supplement treatment has recently become commonly used worldwide. GH treatment contributes to improvements in height, body composition, bone density and breathing functions in PWS [3]. Recently, we consider that there has been a decrease in severely obese patients with PWS.

In this study, we investigated patients who had undergone surgery for scoliosis (Cobb angle of >45 degrees) in PWS, in comparison with conventional surgical reports.

Materials and methods

There were 136 PWS patients being followed-up from November 2002 to August 2009 by the Department of Pediatrics at Dokkyo Medical University Koshigaya Hospital. All the patients were diagnosed using fluorescence in situ hybridization or methylation tests. Scoliosis was identified in 39 patients (31%), of whom 13 patients had Cobb angles of >45 degrees. We investigated nine of these patients (four males and five females) who had undergone surgery. Their mean age was 11 years (range 4–20 years). Six patients had an inherited deletion of chromosome 15q11–13 and three patients did not have a deletion. We focused on the following two aspects: (1) the body mass using the body mass index (BMI), presence of mental retardation, presence and periods of GH supplement treatment, presence of brace treatment and type of scoliosis curve; and (2) the surgical methods, blood loss, operation time, presence of autologous blood transfusion, presence of allogeneic blood transfusion, complications and changes in the Cobb angle and kyphosis angle (before surgery, after surgery and at final follow-up).

Results

The mean follow-up period was 6 years 10 months (range 9–153 months). Regarding the clinical characteristics, the average BMI was 22.5 kg/m^2 , and the individual BMIs reflected 4 thin patients (BMI: $<18.5 \text{ kg/m}^2$), 2 average-sized patients (BMI: $18.5\text{--}25.0 \text{ kg/m}^2$), 1 slightly obese patient (BMI: $25.0\text{--}30.0 \text{ kg/m}^2$) and 1 severely obese patient (BMI: $>30.0 \text{ kg/m}^2$). Mental retardation was found in all patients. GH therapy was administered in eight of the nine patients, and the mean preoperative period of GH therapy was 5.0 years. Brace treatment was only performed in two patients. The types of scoliosis curves were classified by the methods of Lenke et al. [4] and are shown in Table 1.

Regarding the surgical characteristics, spinal correction and fusion were performed in six patients (anterior method in three patients; posterior method in three patients) at the

initial surgery, and the growing rod method was performed in three patients. Necessary additional operations were performed in two patients for additional correction and fusion surgery owing to progressive scoliosis at the upper end of the fused level. In the total 11 surgeries performed in the 9 patients, the mean blood loss was 397 ml (range 150–900 ml) and the mean operation time was 4 h 20 min. Allogeneic blood transfusion was performed in one patient. Autologous blood transfusion was performed in five surgeries for four patients. Regarding complications, one patient experienced early dislodgment of the hook after the first surgery and one patient experienced a superior wound infection. However, there were no dangerous complications such as deep infections or neurovascular damage (Table 2). The mean Cobb angles were 76.0 degrees (range 45–85 degrees) before surgery, 34.6 degrees (range 13–55 degrees) after surgery and 35.8 degrees (range 15–55 degrees) at follow-up (Table 3).

Case 1

Case 1 was a 5-year-old girl. She was diagnosed with a hereditary form of PWS with deletion of chromosome 15q11–13 at 1 year of age. GH supplement treatment (1.8 mg/week) and a diet therapy were started when she was 2 years 6 months. Scoliosis was observed in this patient at 3 years of age, and she was subsequently introduced to our Orthopedics Department. The Cobb angle was 29 degrees at T10–L4 and the sagittal alignment was 19 degrees at T10–L4 at the first consultation. However, the scoliosis deteriorated to 80 degrees at T10–L4 and the sagittal alignment was 32 degrees of kyphosis at T1–T12 and 33 degrees of lordosis at L1–S1 at 5 years of age. We tried to use an under-arm brace treatment during the observation period, but she hated the brace because of her mental retardation and was unable to put it on. At the time of surgery, her height was 96.0 cm, her weight was 14.8 kg and her BMI was 16.1 kg/m^2 . There were no abnormal data in blood analyses and no neurological deficits. There were also no abnormal findings by CT or by MRI including anomalies and deformities of the spinal cord and vertebrae. The GH supplement treatment had been performed for 3 years 3 months before surgery. Anterior correction and fusion were performed with the Mykres system of spinal instrumentation. After the surgery, the scoliosis was corrected to a Cobb angle of 22 degrees and the sagittal alignment was 16 degrees of lordosis at T10–L4. The quantity of bleeding was 229 ml and the operation time was 3 h 54 min. At 4 years after surgery, the Cobb angle was 35 degrees at T10–L4, with 23 degrees of kyphosis at T1–T12 and 34 degrees of kyphosis at L1–S1 (Fig. 1).

Table 1 Preoperative data

Age (years old)/gender		Presence of GH treatment (periods: years and months)	Type of scoliosis	BMI (kg/m ²)	Brace treatment	Follow-up period (years and months)
At surgery	At onset of scoliosis					
5/F	3	3 years 3 months	6C	16.1	Impossible	75
15/M	4	5 years 2 months	3C	17.0	Impossible	67
17/M	16	4 years 8 months	2C	17.0	Possible	113
11/F	4	5 years 2 months	3C	24.5	Impossible	21
15/M	14	8 years 11 months	5C	20.3	Impossible	60
8/F	1	–	2C	40.9	Impossible	153
11/M	7	5 years 6 months	3B	15.2	Impossible	77
17/M	15	8 years 10 months	5C	29.2	Impossible	120
5/F	1	2 years 3 months	1C	15.7	Possible	12

The types of scoliosis were classified by the Lenke classification [4]

GH growth hormone; BMI body mass index

Table 2 Surgical data

Age/ gender at surgery	Surgical methods	Instrumentation	Surgical level	Blood loss	Operation time (hours, minutes)	Autologous blood transfusion (ml)	Allogeneic blood transfusion (ml)	Complications and additional surgery
5/F	ACF	Mykres	T11–L3	229	3'54"	Impossible	None	None
15/M	1st: PCF	Mykres	T3–L3	860	5'11"	600	800	L3 screw pulled out
16/M	2nd: PCF	Mykres	T3–L4	210	3'30"	None	None	None
17/M	PCF	Mykres	T3–L3	900	4'40"	600	None	Superior infection
11/F	Growing rod	Mykres	T2–L3	250	3'00"	Impossible	None	Early hook dislodgment
15/M	ACF	Mykres	T12–L2	260	4'10"	Impossible	None	None
8/F	1st: ACF	Zeilke	T10–L2	300	4'32"	600	None	Progress, upper fused level
19/F	2nd: PCF	Legacy	T1–L1	650	5'19"	1,030	None	None
11/M	Growing rod	Mykres	T12–L1	120	2'20"	Impossible	None	None
17/M	PCF	Mykres	T3–L3	440	7'20"	1,200	None	None
5/F	Growing rod	Mykres	T2–L2	150	3'43"	Impossible	None	None

ACF anterior correction fusion, PCF posterior correction fusion, 1st first surgery, 2nd second surgery

Cases with distraction surgery using the growing rod method are excluded

Case 2

Case 2 was a 17-year-old boy. He was diagnosed with a hereditary form of PWS with uniparental disomy in the Pediatrics Department of our hospital at 3 years of age. GH supplement treatment (4.6 mg/week) and a diet therapy were started when he was 8 years 6 months. Scoliosis was observed in this patient at 15 years of age, and he was subsequently introduced to our Orthopedics Department. The Cobb angle was 35 degrees at T9–L4 at the first consultation. However, the scoliosis deteriorated to a double curve with Cobb angles of 45 degrees at T4–T9 and 52 degrees at T9–L3 and the sagittal alignment was 32 degrees at T1–T12 and 31 degrees at L1–S1 at 17 years of age. We tried to use an under-arm brace treatment during

the observation period, but he hated the brace owing to his mental retardation and was unable to put it on. At the time of surgery, his height was 157.9 cm, his weight was 72.8 kg and his BMI was 29.2 kg/m². There were no abnormal data in blood analyses and no neurological deficits. There were also no abnormal findings by CT or by MRI including anomalies and deformities of the spinal cord and vertebrae. The GH supplement treatment had been performed for 8 years 10 months before surgery. Posterior correction was performed with the Mykres system of spinal instrumentation at T3–L3. After the surgery, the scoliosis was corrected to Cobb angles of 13 degrees at T4–T9 and 13 degrees at T9–L3, and the sagittal alignment was 35 degrees of kyphosis at T1–T12 and 9 degrees of lordosis at L1–S1. The quantity of bleeding was 440 ml and the

Table 3 Radiographic data

Age/gender at surgery	Level	Major curve (Cobb angle)			T1–T12 (Kyphosis)		L1–S1 (lordosis)	
		Presurgery	Postsurgery	Final F/U	Preoperative	Final F/U	Preoperative	Final F/U
5/F	T10–L4	80	22	35	32	23	33	34
15/M	T3–12	69	35	40	4.7	35	20	27
17/M	T8–L3	47	27	27	20	43	34	34
11/F	T10–L4	72	44	57	18	46	31	40
15/M	T6–T10	46	36	40	28	38	26	30
	T10–L3	59	39	39				
8/F	T2–T7	71	45	45	34	53	26	49
	T7–L2	71	55	55				
11/F	T4–L1	53	27	27	31	30	33	32
17/M	T4–T9	45	13	16	32	35	31	9
	T9–L3	52	13	15				
5/F	T6–L1	65	40	26	55	46	52	46

The values are in degrees

F/U follow-up

Fig. 1 Case with anterior correction and fusion. **a** Before surgery. **b** After surgery. **c** Final follow-up

operation time was 7 h 20 min. At 1 year after the surgery, the Cobb angles were 16 degrees at T4–T9 and 15 degrees at T9–L3. These results were good without any correction loss (Fig. 2).

Case 3

Case 3 was an 11-year-old boy. He was diagnosed with a hereditary form of PWS with deletion of chromosome

Fig. 2 Case with posterior correction. **a** Before surgery. **b** After surgery. **c** Final follow-up

15q11–13 soon after birth. GH supplement treatment (4 mg/week) and a diet therapy were started when he was 5 years 11 months. Scoliosis was observed in this patient at 7 years of age, and he was subsequently introduced to our Orthopedics Department. The Cobb angle was 37 degrees at T6–L1 at the first consultation. However, the scoliosis deteriorated to a Cobb angle of 55 degrees at T2–L3 and the sagittal alignment was 31 degrees of kyphosis at T1–T12 and 33 degrees of lordosis at L1–S1 at 11 years of age. We tried to use an under-arm brace treatment during the observation period, but he hated the brace owing to his mental retardation and was unable to put it on. At the time of surgery, his height was 148 cm, his weight was 72 kg, his BMI was 15.2 kg/m² and he had leptosomatic habitus. There were no abnormal data in blood analyses and no neurological deficits. There were also no abnormal findings by CT or by MRI including anomalies and deformities of the spinal cord and vertebrae. The GH supplement treatment had been performed for 5 years 6 months before surgery. In consideration of his bone fragility, we performed the growing rod method, which can maintain growth, and it was planned with two stages of surgery to produce a stronger anchor. In the first surgery, a hook was anchored in the upper edge region and a screw was attached at the lower edge, and autologous iliac bone was only transplanted on the edges. After 6 months, a strong

anchor was confirmed with bone fusion. Next, posterior correction was performed with the Mykres system of spinal instrumentation at T2–L1. A straight tandem connector was used at the thoracolumbar area, and the hook and pedicle screw with the strong anchor through bone fusion were connected with a rod. After this surgery, the scoliosis was corrected to a Cobb angle of 27 degrees and the sagittal alignment was 30 degrees of kyphosis at T1–T12. The quantity of bleeding was 120 ml and the operation time was 2 h 20 min. A doctor from the Department of Pediatrics provided mental support to the patient both preoperatively and postoperatively. Presently, rod extension of 1.5 cm is still being continued every 6 months (Fig. 3).

Discussion

Holm and Laurnen [5] reported that the spinal curvatures in 15–20% of the PWS patients eventually require surgical management. In our study, the frequency of patients who needed surgery was 9.6% (13/136). Accadbled et al. [2] described 16 patients who underwent surgery from 1997 to 2004 for scoliosis in PWS. Regarding complications, there were nine major complications, including four cases of severe kyphosis above the fusion, two deep infections and one transient paraplegia. The four kyphosis cases required

Fig. 3 Case with the growing rod procedure. **a** Preoperative photograph and X-ray. **b** After surgery. **c** Final follow-up. **d** Height in PWS male with respect to age. Weight in PWS male with respect to age

reoperations, three of which were for complications involving permanent spinal cord injury. In that study, GH supplement treatment was administered to 7 of the 16 patients, but most of the patients were obese. Furthermore, the surgeries involved the use of Harrington or Luque instrumentations, which are no longer used.

Weiss and Goodall [6] performed a systematic review in 2009, and concluded that the rate of complications after spinal fusion in patients with scoliosis in PWS was very high and that their death rates were higher than those of patients with adolescent idiopathic scoliosis. Furthermore, the long-term side-effects of the interventions were detrimental, such that the risk–benefit ratios favored conservative approaches over spinal fusion surgery.

As a cause of suffering after surgery for scoliosis in PWS, Rees et al. [1] reported that postoperative respiratory complications can become serious owing to restrictive respiratory disorders caused by the severe obesity peculiar to PWS, deterioration of the quantity of ventilation by the small height and imperfect function of the respiratory muscles with myopathy. Furthermore, they pointed out that preoperative breathing function training is difficult in PWS patients because of their mental retardation. They further stated that a bleeding tendency is brought on by weakness of the blood vessel walls owing to connective tissue abnormalities. In addition, we were concerned about the risk of surgery because there is higher risk of infection associated with the high frequency of diabetes in PWS.

Nohara et al. [7] reported a case of a 14-year-old patient who was severely obese (BMI: 34.4 kg/m²) and had obstructive pulmonary disease and sleep apnea. After correction surgery, breathing control by a ventilator was required owing to atelectasis for 13 days. In addition, Kakutani et al. [8] described a case of a 17-year-old boy who was severely obese (BMI: 37.5 kg/m²) and had a Cobb angle of 75 degrees at T10–L3 with a very rigid spinal deformity. In that report, the authors had hoped to operate by anterior release, posterior correction and fusion. However, anterior release was impossible because of a restrictive pulmonary disorder caused by the severe obesity. The authors described that the correction could not be achieved at a satisfactory level, because only posterior correction was able to be performed. However, Tokutomi et al. [9] reported a case of cardiopulmonary impairment caused by severe kyphoscoliosis in PWS. A breathing function imperfection can decrease the quality of life of PWS patients with severe kyphoscoliosis. We need to make a greater effort to improve the surgical outcomes.

On the other hand, Gurd and Thompson [10] described an operation for scoliosis in PWS in a 7-year-old girl. They reported that the girl underwent surgery although her laminas were too weak to hold a Harrington rod. In a recent report from Japan, Yamada et al. [11] reported that a

patient with Cobb angles of 43 degrees at T1–T5, 60 degrees at T5–T11 and 52 degrees at T11–L4 was successfully treated surgically using modern instrumentation (XIS-SS system) via a posterior approach. Nohara et al. [7] reported good results in a 12-year-old girl with PWS who had a BMI of 21.4 kg/m² and a Cobb angle of the main curve of 106 degrees at T6–L1. A Smith-Petersen osteotomy at T2–L3, anterior release at T7–T12 and correction and fusion at T6–T10 were performed in this patient. After the surgery, the Cobb angle was corrected to 20 degrees and the correction rate was 82%. In addition, Kakutani et al. [8] reported that T12–L3 anterior correction fusion was performed in an 11-year-old girl. Her BMI was 23 kg/m² and the quantity of bleeding was 477 ml. Her Cobb angle was corrected to 23 degrees postoperatively from 69 degrees preoperatively without any complications.

There are reports about difficulties associated with management connected with the severe obesity that is peculiar to PWS, as well as difficulties associated with breathing management and mental retardation. Therefore, surgery remains controversial in PWS based on previous reports, considering that there are high rates of complications in patients with PWS undergoing surgery and the health-related benefits of such surgery in these patients are unclear. It is difficult to make clear decisions regarding the optimal approaches for surgical treatment or conservative treatment for PWS patients. Indications for surgery are necessary to determine individual cases.

Recently, the treatment of PWS has improved remarkably in the field of pediatrics. GH supplement treatment was started in Japan in January 2001, and many reports have described its utility and positive effects such as height acceleration, body mass reduction and muscular strength improvement worldwide. However, there are some concerns regarding the risks involved in GH treatment of PWS patients. First, there was a report of sudden death owing to the use of GH treatment [12]. Although the relationship between the sudden death and GH treatment was completely unclear, Nagai et al. [13] subsequently reported that the causes of sudden unexpected death did not differ between PWS patients with or without GH treatment. GH treatment has now become contraindicated for patients who are seriously obese or have a high breathing obstacle. Therefore, careful use of GH treatment is necessary in PWS patients.

Second, the possibility of deterioration in scoliosis was suggested, although we have particularly reported that there was no connection between the frequencies of scoliosis in GH treatment and non-treatment groups [14, 15]. Based on the backgrounds of these studies, GH treatment has recently been recommended at an early age, and it is assumed that its long-term use is not a problem. It is important that PWS patients are treated intensively from 3 years of age, because obesity begins at around this time.

GH supplement treatment is effective for height acquisition, body composition improvement, natural activity and muscular strength improvement, but the greatest purpose of GH use is body composition improvement. All of our patients except one were treated with long-term GH supplement treatment in the Department of Pediatrics from childhood.

Recently, a sex hormone supplement treatment has also been shown to be effective for body composition, mental and bone density improvements. Osteoporosis is caused by imperfect sex hormone secretion in PWS, and this symptom was reported to lead to a risk of more than 29% for a bone fracture once in the lifetime of PWS patients [16]. Preoperatively, improvement in the bone density is important.

Regarding complications, only early dislodgment of the hook and a superior infection were encountered. Fortunately, there were no dangerous complications such as neurological deficits, vascular damage or deep infections. However, an additional operation was performed in two patients. One patient was an 8-year-old girl whose surgery only involved anterior fusion around the apex of the scoliosis to restrain its progression. After 11 years, the kyphoscoliosis had deteriorated at the upper fused level. Accadbled et al. [2] also reported that 4 of 16 patients had progression of serious kyphosis at the upper fused level during their follow-up periods. In our case, the growing rod method was indicated at the present time. In the other case, a screw had been pulled out at the lowest level of the correction level. This patient underwent surgery using sublamina wiring by a polyethylene tape. However, it was considered that the influence of osteopenia and uncontrolled behavior associated with the mental retardation contributed to the loose screw.

Fortunately, the operative outcomes in our patients were better than in those of some other reports [5, 6]. Some reasons are: first, the Pediatrics Department provided intense preoperative therapy with GH supplement treatment, sex hormone supplement treatment, diet and so on for a long term owing to the completely uncontrolled general conditions in all patients. As a result, the patients had a reduced BMI and improved bone density before surgery. Although breathing function evaluation was difficult because all PWS patients have mental retardation, our patients can be expected to show improvements in their breathing functions. In our patients, we operated using anterior correction fusion. If patients are not obese and do not have breathing function imperfections, surgeons will be able to perform anterior surgery. Therefore, the GH supplement treatment administered was a very effective therapy. In other words, the GH supplement treatment reduced the surgical risk in PWS patients. Consequently, spinal surgeons are able to choose greater ranges of operative methods for successful correction fusion for difficult cases.

Second, in our institution, the spinal surgeons were supported in the preoperative and postoperative therapies by pediatricians who had abundant experience of PWS patients. In addition, there was cooperation by the families of the patients who were well educated about the characteristics of PWS by their pediatricians. Sometimes PWS patients exhibited uncontrolled behavior for orthopedics preoperatively or postoperatively owing to their mental retardation. It is considered that these supports were necessary for smooth treatment. Therefore, the medical team care of orthopedic surgeons and pediatricians was indispensable for the treatment of this disease.

Recently, the dual growing rod technique [17] has been developed. Since all PWS patients have mental retardation, many of them hate brace treatment. In our patients, the brace-wearing rate was low (2/9). When these patients are infants and young children, corrective surgery is required. The dual growing rod technique was found to be an effective method. However, this method requires a lot of distraction surgery to maintain steady growth.

With the development of spinal instrumentation for pediatric surgery, instrumentation for the growing rod method was developed using the strong claw technique, thereby enabling a low profile with an increase in the correction power. In addition, a tandem connector for infants was developed, meaning that the distraction surgery became less invasive. Subsequently, we devised a better technique for the growing rod method of spinal correction, so that we could obtain a strong anchor production for bone fragility in infants or young children. The resulting spinal corrective surgery was separated into two operations. First, anchor production alone was performed with a hook at the upper end, a pedicle screw at the lower end and a bone graft from the autologous iliac bone. After the anchors became strong with complete bone fusion, correction fusion surgery was performed in a second operation.

It is considered that the device for anchor formation that leads to stronger bone fusion was effective for avoiding early dislodgment of the hooks in patients who had bone fragility as infants or young children.

Conclusions

In this study, the frequency of patients with PWS who required surgery in this study was 9.6% (13/136). GH therapy was administered in eight of the nine patients examined who underwent surgery. The mean BMI was 22.5 kg/m², and a few obese patients underwent surgery. Regarding complications, one patient experienced early dislodgment of the hook and one patient experienced a superior wound infection. There were no severe complications such as deep infections or neurovascular damage.

Therefore, we consider that GH treatment before surgery may reduce postoperative complications. Brace treatment was only performed in two of the nine patients. The growing rod method was effective for PWS patients who resisted brace treatment owing to mental retardation.

Conflict of interest None of the authors has any potential conflict of interest.

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