 American Journal of Medical Genetics Part A 146A:873–880 (2008)

Developmental Profiles in Young Children With Prader–Labhart–Willi Syndrome: Effects of Weight and Therapy With Growth Hormone or Coenzyme Q_{10}

Urs Eiholzer,[1]* Udo Meinhardt,[1] Valentin Rousson,[2] Nelica Petrovic,[1] Michael Schlumpf,[1] and Dagmar l'Allemand[1]

[1]Center for Pediatric Endocrinology Zurich (PEZZ), Zurich, Switzerland
[2]Department of Biostatistics, University of Zurich, Zurich, Switzerland

Received 12 February 2007; Accepted 17 September 2007

Muscle hypotonia and failure to thrive are key symptoms of Prader–Willi syndrome (PWS) allowing diagnosis during infancy already. Improved general care as well as Coenzyme Q_{10} (CoQ_{10}) and growth hormone (GH) are administered to improve PWS children's outcome. This study aims to investigate psychomotor development of young PWS children in relation to body weight and body composition at baseline as well as to the effects of GH or CoQ_{10} therapy. Twenty-six young children (age 1.0 ± 0.1 years, mean ± SEM) with PWS genetically proven at age 0.1 ± 0.1 years (17 deletions, 8 maternal disomy) were divided into three groups: Group 1 on GH therapy (started in 1994–1996, 6 mg/kg/week) tolerating low body weight (<50th centile), group 2 on GH (1997–2000) and group 3 on CoQ_{10} (2001–2002, 2.5 mg/kg/day orally), both combined with active early weight management to achieve weight >50th centile. Anthropometry, body composition and Griffith's developmental scores (DQs) were assessed before therapy and after 12 months. DQs were not related to infants' weight, lean mass or genetic background. DQs improved significantly with chronological age and were best in the most recently diagnosed group. Improved psychomotor development, mainly due to progress in locomotor development, did not differ between GH and CoQ_{10} treated groups. In conclusion, while only GH has significant effects on growth and body composition, GH and CoQ_{10} therapy act equally on psychomotor development of PWS infants. However, improving psychomotor development may merely reflect an age-related phenomenon additionally depending on early diagnosis and introduction of appropriate care.

Key words: Prader–Willi syndrome (PWS); psychomotor development; body weight; body composition; lean mass; fat mass; growth hormone therapy; coenzyme Q_{10} therapy

How to cite this article: Eiholzer U, Meinhardt U, Rousson V, Petrovic N, Schlumpf M, l'Allemand D. 2008. Developmental profiles in young children with Prader–Labhart–Willi syndrome: Effects of weight and therapy with growth hormone or coenzyme Q_{10}. Am J Med Genet Part A 146A:873–880.

INTRODUCTION

As discussed in Prader's original description of the syndrome [Prader et al., 1956] Prader–Willi syndrome (PWS) can be diagnosed in the newborn child. These children typically present with muscle hypotonia and hypogenitalism [Gillessen-Kaesbach et al., 1995; Miller et al., 1999; Gunay-Aygun et al., 2001; Whittington et al., 2002]. Other early features are psychomotor developmental delay and major feeding difficulties often leading to poor weight gain. In the course of this disorder these children become obese and have behavioral abnormalities. Morbid obesity [Holland et al., 1995; Lindgren et al., 2000] and progressive behavioral abnormalities together with cognitive deficits [Whitman and Accardo, 1987; Malich et al., 2000; Clarke et al., 2002] are a major challenge in the care of children with PWS. The functional abnormalities like disturbance of energy regulation, sleep-related breathing disorders, temperature instability, short stature due to growth hormone (GH) insufficiency (reviewed in Burman et al. [2001] and Eiholzer and Whitman [2004]) and hypogonadism [Eiholzer et al., 2006] result from hypothalamic dysregulation [Prader et al., 1956; Eiholzer, 2001]. While hypogonadism and GH deficiency can be efficiently treated with hormone replacement therapy, there is no specific therapy for

*Correspondence to: Dr. Urs Eiholzer, Center for Pediatric Endocrinology Zurich (PEZZ), Moehrlistrasse 69, CH-8006 Zürich, Switzerland.
E-mail: mail@pezz.ch
DOI 10.1002/ajmg.a.32137

the other abnormalities [Whitman, 2003; Eiholzer and Whitman, 2004].

During the last decade, there was a considerable progress in the knowledge on pathophysiology and natural history of PWS, suggesting that it is crucial to diagnose PWS and to start treatment as early as possible [Vogels and Fryns, 2004]. Early diagnosis leads to early intervention including enhancement of physical activity, special education, and psychological support of the families [Eiholzer, 2001; Eiholzer et al., 2003; Butler et al., 2006; Schlumpf et al., 2006], improving health status and psychosocial development in these patients [Vogels and Fryns, 2004]. While in the first years of management of PWS, a body weight in the lower normal range was tolerated during infancy, a more active weight management, for example by tube feeding, was suggested to improve lean mass and growth (personal communication of O. Trygstad, Norway). In addition, GH replacement therapy not only improves weight and body composition [Carrel et al., 1999, 2004; Myers et al., 2000; Eiholzer et al., 2000b, 2004, 2006], but also motor development in young children [Eiholzer et al., 2000c; Carrel et al., 2004]. GH therapy was even claimed preventing behavioral deterioration in 4–16 years old children with PWS [Whitman et al., 2002] and improving speech development together with cognitive functioning in 15 months old children [Myers et al., 2007].

Another, non-hormonal drug therapy used in PWS children is coenzyme Q_{10}, (CoQ_{10}). CoQ_{10} serum levels were found to be reduced in obese subjects with and without PWS [Butler et al., 2003]. CoQ_{10} transfers electrons within the mitochondrial respiratory chain, acts as antioxidant and regulates physiochemical properties of mitochondrial and other membranes. Therefore, CoQ_{10} is used in neuropediatrics, for example to treat mitochondrial myopathy. It was further suggested that treatment with CoQ_{10} enhances muscle tone and physical activity in infants with PWS (WV Judy, Southeastern Institute of Biomedical research, U.S., personal communication). The beneficial effect of a treatment with CoQ_{10} in infants with PWS, however, is unproven.

Our hypothesis was that in infants with PWS improvement of body weight and body composition is associated with better psychomotor development and that as a consequence, not only early active weight management, but also early GH therapy or CoQ_{10} supplementation stimulate psychomotor development. Thus our observational retrospective study is aimed at investigating the effects of the following variables on psychomotor development of PWS infants: (a) body weight and body composition, (b) date of diagnosis, representing the intensity of comprehensive care and weight management, and (c) therapy with GH or CoQ_{10}.

METHODS

In this observational study, a retrospective longitudinal group comparison, a total of 26 infants and toddlers with genetically proven PWS were studied. All measurements were performed by a single investigator (UE). In most cases, PWS was diagnosed during the first 2 months of life. Feeding difficulties were encountered in all newborns to a differing degree, often persisting into infancy. From 1997 on, extreme attention was paid to improving body weight at least up to the 50th centile of weight for height (WfH $\geq$ 0 SDS). Management of these children included tube feeding, continuous nutrition counseling, physiotherapy and special education teaching. Infants were divided into three groups according to the period of care and mode of management (Table I): Group 1 included infants started on GH therapy between 1994 and 1996 with WfH below 0 SDS. Group 2 included infants started on GH therapy between1997 and 2000, profiting from active

TABLE I. Baseline Data Comparing Growth Hormone (GH) and Coenzyme Q_{10} (CoQ_{10}) Treatment Groups (Means ± SEM; for Age at Diagnosis Median (Range))

Group	1	2	3
Start of GH or CoQ_{10} therapy	1994–1996	1997–2000	2001–2002
Age at diagnosis (years)	0.03 (0–0.34)	0.02 (0–1.83)	0.01 (0–0.39)
Medication	GH	GH	CoQ_{10}
n (m/f)	6 (3/3)	12 (5/7)	8 (6/2)
Age (years)	0.73 ± 0.10	1.30 ± 0.20	0.60 ± 0.20*
Height (SDS)	−2.0 ± 0.6	−2.5 ± 0.5	−1.7 ± 0.4
Weight for height (SDS)	−2.0 ± 0.3**	−0.9 ± 0.4	−1.0 ± 0.4
Genotype (paternal deletion/maternal disomy/imprinting mutation) of n = 25	4/2/0	9/3/0	4/3/0
Gestational age (weeks) 39 (31–42)	37.6 ± 1.6	39.7 ± 0.5	39.1 ± 0.8
APGAR score sum (max. 30)	24.5 ± 1.5	21.0 ± 1.56	23.4 ± 2.2
Birth length (SDS)	−2.31 ± 0.82	−0.82 ± 0.30	−1.70 ± 0.37
Birth weight (SDS)	−2.27 ± 0.74	−1.54 ± 0.12	−1.87 ± 0.41

*$P < 0.05$ compared to group 2 and combined group 1 and 2.
**$P = 0.075$ compared to group 2.

weight management aiming for normal weight gain. In infants of group 1 and 2 GH therapy was started after the initial investigation (Genotropin®, Pfizer, Duebendorf, Switzerland, subcutaneous daily injections of 6 mg/m^2/week corresponding to 0.025 mg/kg/day). Group 3 included infants started on CoQ_{10} therapy after the year 2000 (Sanomit®, 2.5 mg/kg/day orally, MSE, Bad Homburg, Germany) for 1 year before switching to GH thereafter (dose as mentioned above) and weight management identical to group 2.

Family history was negative for mental or neurological diseases, social background was middle-class on average and free from unfavorable conditions. Information on birth weight, length and delivery complications (APGAR score) is provided in Table I, there were no differences between the three groups. Besides cryptorchidism in the majority of the boys and scoliosis in two children, overall health status was normal. The level of medical care was similar in all children, because there is the same basic insurance system in all patients in Switzerland, providing necessary medical and psychological therapies in the patients and their families.

Height, weight, body composition, and psychomotor development were measured before, after 6 and 12 months of GH or CoQ_{10} therapy. Height and weight were measured using standard techniques [Prader et al., 1989] and expressed as age and gender adjusted standard deviation scores (SDS) based on reference data of the 1st Zurich Longitudinal Study [Prader et al., 1989]. As a measure of obesity weight was related to height (weight for height, WfH). Because of the initial presentation with short stature and subsequent catch up growth, WfH was shown to be superior to BMI to represent adiposity in PWS children [Eiholzer et al., 2000b]. Body composition was derived from total body water determined by stable isotope dilution [Eiholzer et al., 2004]. Lean mass (LM) was calculated from total body water as published earlier [Fusch et al., 1993]. Fat mass (FM) was computed by subtracting LM from total body weight, and relative fat mass (%FM) by dividing fat mass × 100 by total body weight. Body composition measurements were expressed as SDS based on healthy children [Fusch et al., 1993] matched for height and gender [Eiholzer et al., 2000b]. Body composition measurements were available for 12 infants of group 2 and 6 infants of group 3 only. Psychomotor development was assessed by the Griffith test. This developmental test is widely used in central Europe. It can be performed by specially trained pediatricians in children between 1 and 24 months in the presence of their parents, and to a higher age in children with developmental disabilities. The German edition was validated in German children by Brandt [1983]. Developmental quotients are expressed in percent of the median of age-related references: Global DQ for global development, DQ A for the scales of locomotion, DQ B for personal-social development, DQ C for hearing and speech, DQ D for hand and eye and DQ E for cognitive performance, all consisting of 24 items except for DQ A with 22 items.

Early GH therapy and the related investigations were prospectively approved by the local Ethic's Committee of the Children's University Hospital of Zurich.

All data were processed by GAS 5.021, a database system (Institute for Medical Informatics, Zurich, Switzerland). Data are presented as means and standard errors of the mean (SEM). Differences within the groups were assessed by using the nonparametric Wilcoxon signed rank test for paired samples. Differences between the groups were identified by the Mann–Whitney *U* test at baseline and after 12 months. The results obtained at 0, 6, and 12 months were completely assessed in 21 children and compared by ANOVA for repeated measurements, allowing to test for changes during therapy (factor Time), for differences between the groups in the level (factor Group) and in the pattern of the longitudinal profiles in each group (interaction Time × Group). *P* values for factor Time and interaction Time × Group were corrected according to Greenhouse-Geisser. Correlations were assessed by the Spearman's rank correlation test. *P* values below 0.05 were considered as being statistically significant.

RESULTS

Genotype, Gender, and Phenotype

At baseline, there was no difference in any parameter between children with paternal deletion (n = 17) and with maternal unidisomy (n = 8, Table I), on the one hand, and between boys and girls, on the other. Also with regard to perinatal conditions (Table I), no significant differences between the groups were found.

Anthropometry

Before starting GH or CoQ_{10} therapy, children in group 3 were significantly younger compared to children in the combined GH treated group (1 and 2) and height SDS were low in all groups without being different between the groups (Table I). On therapy height SDS increased significantly in the two GH treated groups (ANOVA Time $P < 0.0001$), but not in the CoQ_{10} treated group, the difference between the treatments being significant (ANOVA Group × Time $P < 0.01$, Fig. 1). WfH did not differ significantly between the groups, neither before start (Table I), nor on GH and CoQ_{10} therapy. WfH SDS increased similarly in all groups (ANOVA Time $P < 0.01$, Fig. 2).

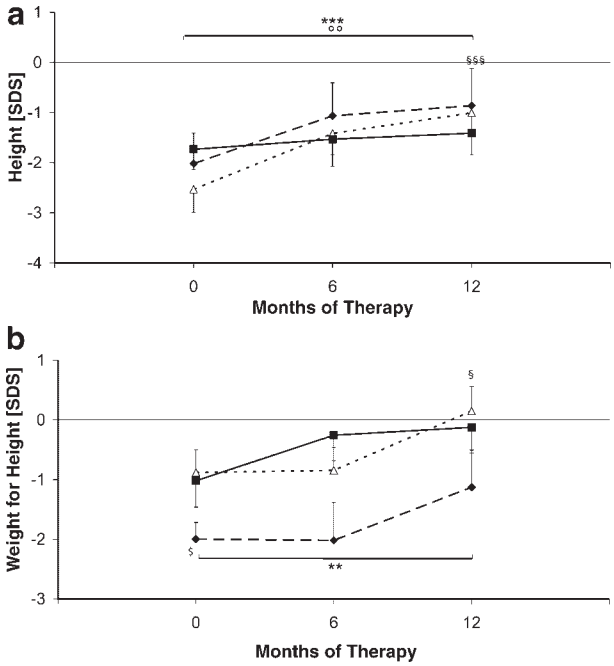

FIG. 1. Twelve-month period of height (**a**) and weight evolution (**b**) in young children with PWS on growth hormone (GH), group 1 (n = 6, broken line with black rhombus) and group 2 (n = 12, dotted line with open triangle) or coenzyme Q10 treatment (group 3, n = 8, full line with black square), means ± SEM. ***·** ANOVA time $P < 0.0001$ or $P < 0.01$, respectively, within the groups and °° ANOVA Group × Time $P < 0.01$, different pattern between the groups. §§§$P < 0.001$ or §$P < 0.05$ significant changes between 0 and 12 months within the combined group 1 and 2. §$P = 0.06$ trend of difference between group 1and 2 before therapy.

Body Composition

Before starting GH or CoQ_{10} therapy FM SDS and %FM SDS were equally high and LM SDS equally low in both groups examined (group 2 and 3). In the CoQ10 treated group but not in the GH treated group FM SDS increased and LM SDS decreased when comparing 0 and 12 months results (Table II).

Developmental Quotients

At baseline in the three groups mean global developmental quotient (DQ) ranked between 54% and 66% of the reference mean and did not differ between the groups (Fig. 2). On therapy global DQ increased in all groups without being different between the groups (ANOVA Time $P = 0.015$, Fig. 2a). Among all partial skills tested the locomotor function (DQ A) ranked the lowest before therapy (on average between 30% and 44% of the references, Fig. 2b) without being different between the groups. Even though DQ A increased highly significantly over time in all groups without difference between them (ANOVA Time $P = 0.001$), it remained low (<80%). At baseline the personal-social development (DQ B) in the three groups ranked between 60% and 80%. The CoQ_{10} treated group had significantly higher DQ B than the combined GH treated groups both at baseline and throughout the study (ANOVA Group $P = 0.041$). There was no significant change in DQ B over time by ANOVA, but in the combined group 1 and 2 it was significantly higher after 12 months compared to baseline (Fig. 2c). At baseline hearing and speech quotient (DQ C) was uniformly reduced in all groups (around 55% of the reference mean). DQ C increased significantly over time without being different between the groups (ANOVA Time $P = 0.048$, Fig. 2d). Before and during therapy hand and eye development (DQ D) was almost normal in group 3 (81% of the reference mean), being significantly higher compared to the combined GH treated groups both at baseline (68%) and throughout the study (ANOVA Group $P = 0.042$). DQ D however did not change during therapy (Fig. 2e). Before therapy the intellectual performance (DQ E) ranked between 57% and 70%. Throughout the observation period, DQ E was significantly higher in group 3 compared to the combined groups 1 and 2 (70% of the reference mean and 62%, respectively, ANOVA Group $P = 0.024$). DQ E increased similarly in all groups during treatment (ANOVA Time $P = 0.010$, Fig. 2f).

When age-related groups were formed across all patients, before therapy, children 1.3–2.3 years old showed significantly better motor development than infants (0–0.5 years, DQ A 59.9 ± 5.1% vs. 30.6 ± 7.4%, respectively), even though corrected for age, while there were no other significant differences between the age groups.

Correlation Analysis Before Therapy

Based on pooled data of the three groups before therapy, we calculated Spearman correlations between developmental quotients (global DQ, DQ A, DQ B, DQ C, DQ D, and DQ E) and clinical candidate predictors (date of diagnosis, age at diagnosis, age at baseline, WfH SDS, height SDS, LM SDS, FM SDS, and %FM SDS). The older the children, the better was their locomotor development (baseline age vs. DQ A: rho = 0.51, $P < 0.01$). The date of diagnosis correlated positively with DQ B (rho = 0.41, $P < 0.05$) and DQ D (rho = 0.41, $P < 0.05$), meaning that children diagnosed in more recent years scored better on the personal-social and hand-eye scales. While WfH SDS did not correlate with any predictors tested, height SDS correlated positively with both DQ C for speech and hearing (rho = 0.54, $P < 0.01$) and DQ D for hand and eye skills (rho = 0.42, $P < 0.05$). A lower fat mass was associated with a better performance DQ E (rho = −0.515, $P < 0.05$).

DISCUSSION

PWS is often diagnosed only after infancy [Gillessen-Kaesbach et al., 1995; Whittington et al., 2002;

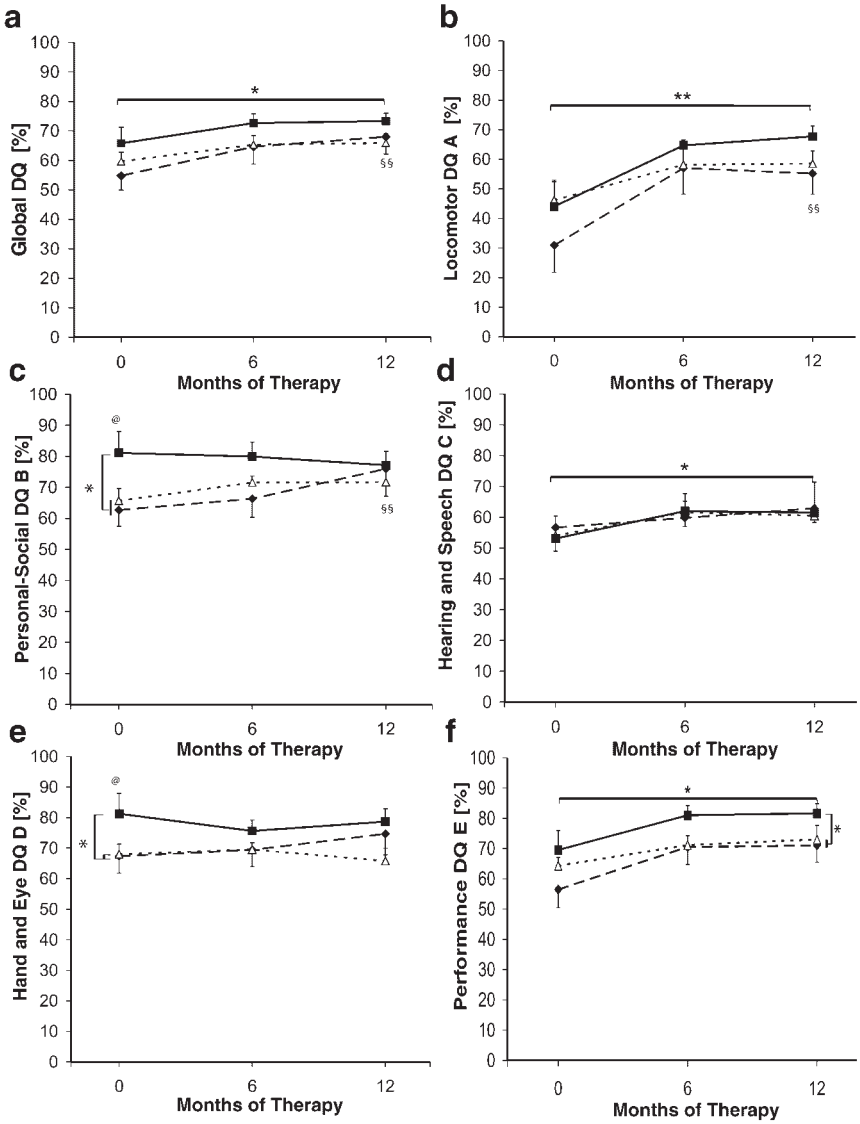

FIG. 2. Developmental quotients (DQ) in young children with PWS during 12 months of therapy with GH (group 1 = broken line with black rhombus, group 2 = dotted line with open triangle) or CoQ_{10} (full line with black square), means ± SEM. Refer to Figure 1 for further explanations. **a**: Global DQ, * ANOVA Time $P < 0.05$, significant and similar increase during therapy in all three groups. $^{\S\S}P < 0.01$ significant change between 0 and 12 months within the combined group 1 and 2. **b**: Locomotor DQ A, ** ANOVA Time $P < 0.01$ refer to (b) for further explanations. **c**: Personal-social DQ B, $^{@}P < 0.05$ significantly higher DQ B in group 3 compared to the combined group 1 and 2 before therapy and throughout the study, * ANOVA Group $P < 0.05$. $^{\S}P < 0.05$ significant change between 0 and 12 months within the combined group 1 and 2. **d**: Hearing and speech developmental DQ C, refer to (b) for explanations. **e**: Hand and eye DQ D, refer to (c) for explanations. **f**: Cognitive performance DQ E, * ANOVA Group and * ANOVA Time $P < 0.05$, higher DQ E in group 3 compared to the combined group 1 and 2 and significant increase during therapy in all groups.

Wigren and Hansen, 2003; Vogels and Fryns, 2004], although the nutritional status during the first year of life is crucial for the later outcome [Ong and Loos, 2006] in terms of cardiovascular risk profile [Ekelund et al., 2006] and cognitive function [Lucas, 1998]. Due to typical neonatal presentation with muscular hypotonia and hypogenitalism, diagnosis is being made earlier in Switzerland compared to other countries [Vogels and Fryns, 2004]. Nevertheless, the number of very young children with PWS available for studies is limited [Bekx et al., 2003; Eiholzer et al., 2004; Myers et al., 2007], because PWS has a very low prevalence of 1: 15,000 up to 1:25,000 [Burd et al., 1990; Whittington et al., 2001; Vogels et al., 2004].

To study how psychomotor development depends on pretreatment anthropometric or genetic parameters and on GH or CoQ10 therapy, PWS children diagnosed between 1994 and 2003 were categorized into three groups according to the year of initiation of GH or CoQ_{10} therapy.

This stratification indirectly included the effects of a secular trend in weight management after 1996: Before starting therapy children of the first group

TABLE II. Body Composition (Mean ± SEM) Adjusted for Height and Gender at 0, 6, and 12 Months of Therapy With Growth Hormone (GH, Group 2) or Coenzyme Q_{10} (CoQ_{10}, Group 3)

Group	0 months	6 months	12 months
2, GH (n = 12)			
Lean mass (SDS_{height})	-1.33 ± 0.13	-1.33 ± 0.25	-0.89 ± 0.27
Fat mass (SDS_{height})	0.98 ± 0.14	0.85 ± 0.38	1.03 ± 0.32
% Fat (SDS_{height})	1.15 ± 0.10	0.84 ± 0.34	0.89 ± 0.25[a]
3, CoQ_{10} (n = 6)			
Lean mass (SDS_{height})	-0.89 ± 0.20[1]	-0.85 ± 0.24	-1.33 ± 0.10[1]
Fat mass (SDS_{height})	0.44 ± 0.31[2]	0.91 ± 0.25	1.48 ± 0.32[2]
% Fat (SDS_{height})	1.02 ± 0.30	1.18 ± 0.17	1.50 ± 0.20[a]

[1,2]Comparing groups with identical indices: $P < 0.05$.
[a]Comparing groups with identical indices: $P = 0.08$.

(1994–1996) often had lower body weight than children treated after 1996. In the past the weight in the lower normal range typically seen in infants with PWS was tolerated hoping to prevent obesity [Stadler, 1995]. As expected and reported previously [Eiholzer et al., 1999, 2004] we found reduced LM in all infants; nevertheless their FM was relatively increased. The body compositional characteristics found in these infants illustrate that the dysregulation of body composition typically seen in PWS is already present at this early age. Based on these results and on studies suggesting impaired neurodevelopment and growth in children with suboptimal nutrition during the critical postnatal phase [Skuse et al., 1994; Lucas, 1998; Schmidt et al., 2001; Latal-Hajnal et al., 2003], early active weight management was introduced in 1997 [Eiholzer and Whitman, 2004]. In the present study improved WfH, however, did not improve short stature, possibly as a consequence of GH insufficiency.

During therapy with CoQ_{10}, growth and body composition deteriorated. In contrast, GH therapy normalized height, improved LM for age and stabilized FM, as it had been shown in other studies [Eiholzer and l'Allemand, 2000; Eiholzer et al., 2000b, 2004; Carrel et al., 2002, 2004]. The increase in WfH, however, does not indicate the quality of changes in body compositional [Eiholzer and l'Allemand, 2000; Eiholzer et al., 2000b; Carrel et al., 2002].

The main finding of the present study was that global DQ improved significantly without being different between GH and CoQ_{10} treated groups. The improved DQ was due to improved subscales, locomotion and speech, both ranking the lowest at baseline and the time course of both not being different between GH and CoQ_{10}. During infancy, children with PWS experience more difficulties in subscales of locomotion and speech compared to other qualities of psychomotor development [Cassidy et al., 1997; Butler et al., 2004]. Both speech and locomotor development are strongly influenced by muscle hypotonia and known to improve spontaneously with age [Prader et al., 1956]. The age dependency of locomotion was confirmed by locomotor DQ being positively correlated with age at onset of therapy. Therefore, the observed improvement of DQ and related subscales simply reflects an age dependent phenomenon, GH or CoQ_{10} therapy exerting a minor or no effect.

Finally, the improved cognitive functioning observed both during CoQ_{10} and GH therapy in the present and during GH therapy in a recent other study [Myers et al., 2007] may be secondary to the spontaneous improvement in motor activity and communication. This means that improved cognitive functioning may not be due to GH therapy but due to age and/or other supportive treatments. The most recently treated and youngest group 3 always showed a better cognitive score than the others. There were no group differences in genetic subtype to explain higher cognitive performance, but the observation that the performance DQ was higher the lower fat mass, points to a successful comprehensive care and stimulation of these patients. The numbers are too small and the developmental tests performed not specific enough to decide, whether onset of therapy at young age, improvement of knowledge on management on infants with PWS, intensity of supportive therapy or psychosocial background are related to a better cognitive development in PWS.

During the study period of GH or CoQ_{10} treatment, personal-social and hand-eye development were unchanged and least affected, as previously published [Eiholzer et al., 2000b]. We found a positive correlation between the date of diagnosis and "personal-social" and "hand-eye" development, suggesting that special education teaching, which was continuously improved in the more recent years [Whitman and Greenswag, 1995; Whitman, 2003; Eiholzer and Whitman, 2004] may improve social and fine motor abilities in PWS. This is supported by the fact that PWS children diagnosed in the most recent years scored highest not only in "personal-social" and "hand-eye" development, but also in the "performance" subscale.

Finally, we found no positive correlation between initial body weight and psychomotor development. This finding is not in line with our initial hypothesis

early active weight management improving psychomotor development. To assess the influence of nutritional status in detail, future studies should be done prospectively and by objective methods.

This study has several weaknesses: The small number of patients is inherent to all studies in age-specific subgroups of patients with rare diseases, but is compensated for in part by the homogenous management by the same physician. As the present study is an observational study in disabled children, the absence of an untreated group is due to the fact that we held it to be unethical to withhold growth hormone from these patients, because there is a hypothalamic insufficiency in growth hormone secretion in PWS [Lindgren et al., 1998; Eiholzer et al., 2000a] and because beneficial effects of GH on growth and body composition had been shown in older children with PWS [Lindgren et al., 1998; Carrel et al., 1999; Eiholzer et al., 2000b]. Finally the 1-year follow-up in our study may be too short to document all effects. To expand sample size and observation period, studies will be continued.

In summary improved psychomotor development, in particular locomotion, does not differ between GH and CoQ_{10} treated groups of infant and young children with PWS. The improvement may only reflect an age-related phenomenon possibly linked with PWS muscle hypotonia spontaneously improving with age, but not related to weight status. Cognitive development is better in the most recently diagnosed group, suggesting that improved comprehensive care including early and special education may be crucial. We therefore conclude that in order to support psychomotor development in PWS children, it may be best to aim for an early diagnosis allowing early introduction of general care. Only for growth hormone, but not for CoQ10, could significant therapeutic effects be clearly demonstrated, namely the improvement of growth and body composition already during infancy.

ACKNOWLEDGMENTS

We are grateful to Mrs. Claudia Weinmann for the coordination of examinations and technical assistance. Our special thanks go to the parents and their PWS children for their great commitment and efforts and to the PWS Association of Switzerland. This study was supported by grants from the Foundation Growth Puberty Adolescence, Zürich and Pfizer, Dübendorf, Switzerland.

REFERENCES

Bekx MT, Carrel AL, Shriver TC, Li Z, Allen DB. 2003. Decreased energy expenditure is caused by abnormal body composition in infants with Prader-Willi Syndrome. J Pediatr 143:372–376.

Brandt I. 1983. Griffiths Entwicklungsskalen zur Beurteilung der Entwicklung in den ersten beiden Lebensjahren. Weinheim & Basel: Beltz Verlag. 121 p.

Burd L, Vesely B, Martsolf J, Korbeshian J. 1990. Prevalence study of Prader-Willi syndrome in North Dakota. Am J Med Genet 37:97–99.

Burman P, Ritzen EM, Lindgren AC. 2001. Endocrine dysfunction in Prader-Willi syndrome: A review with special reference to GH. Endocr Rev 22:787–799.

Butler MG, Dasouki M, Bittel D, Hunter S, Naini A, DiMauro S. 2003. Coenzyme Q10 levels in Prader-Willi syndrome: Comparison with obese and non-obese subjects. Am J Med Genet Part A 119A:168–171.

Butler MG, Bittel DC, Kibiryeva N, Talebizadeh Z, Thompson T. 2004. Behavioral differences among subjects with Prader-Willi syndrome and type I or type II deletion and maternal disomy. Pediatrics 113:565–573.

Butler MG, Lee P, Whitman BY. 2006. Management of Prader-Willi Syndrome. 3rd edition. New York: Springer. 550 p.

Carrel A, Myers S, Whitman B, Allen D. 1999. Growth hormone improves body composition, fat utilization, physical strength and agility in Prader-Willi syndrome: A controlled study. J Pediatr 134:215–221.

Carrel AL, Myers SE, Whitman BY, Allen DB. 2002. Benefits of long-term GH therapy in Prader-Willi syndrome: A 4-year study. J Clin Endocrinol Metab 87:1581–1585.

Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB. 2004. Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. J Pediatr 145:744–749.

Cassidy SB, Forsythe M, Heeger S, Nicholls RD, Schork N, Benn P, Schwartz S. 1997. Comparison of phenotype between patients with Prader-Willi syndrome due to deletion 15q and uniparental disomy 15. Am J Med Genet 68:433–440.

Clarke DJ, Boer H, Whittington J, Holland A, Butler J, Webb T. 2002. Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. Br J Psychiatry 180:358–362.

Eiholzer U. 2001. Prader-Willi syndrome. Effects of human growth hormone treatment. Endocrine Development. Savage, M. O. 1: 1–118. Basel: Karger.

Eiholzer U, l'Allemand D. 2000. Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after four years of therapy. Horm Res 53:185–192.

Eiholzer U, Whitman BY. 2004. A comprehensive team approach to the management of patients with Prader-Willi syndrome. J Pediatr Endocrinol Metab 17:1153–1175.

Eiholzer U, Blum WF, Molinari L. 1999. Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome. J Pediatr 134: 222–225.

Eiholzer U, Bachmann S, l'Allemand D. 2000a. Is there a growth hormone deficiency in PWS? Six arguments to support the presence of a hypothalamic GHD in PWS. Horm Res 53:44–52.

Eiholzer U, l'Allemand D, van der Sluis I, Steinert H, Ellis K. 2000b. Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. Horm Res 53:200–206.

Eiholzer U, Malich S, l'Allemand D. 2000c. Does growth hormone therapy improve motor development in infants with Prader-Willi syndrome? Eur J Pediatr 159:299–301.

Eiholzer U, Nordmann Y, l'Allemand D, Schlumpf M, Schmid S, Kromeyer-Hauschild K. 2003. Improving body composition and physical activity in Prader-Willi Syndrome. J Pediatr 142:73–78.

Eiholzer U, l'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C. 2004. Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. J Pediatr 144:753–758.

Eiholzer U, l'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J, Grüters A, Simoni M. 2006. Hypothalamic and Gonadal components of hypogonadism in boys with Prader-Labhart-Willi syndrome. J Clin Endocrinol Metab 91:892–898.

Ekelund U, Ong K, Linne Y, Neovius M, Brage S, Dunger DB, Wareham NJ, Rossner S. 2007. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J Clin Endocrinol Metab 92:98–103.

Fusch C, Scharrer B, Hungerland E, Moeller H. 1993. Body water, lean body and fat mass of healthy children as measured by deuterium oxide dilution. Isotopenpraxis Environ Health Stud 29:125–131.

Gillessen-Kaesbach G, Gross S, Kaya-Westerloh S, Passarge E, Horsthemke B. 1995. DNA methylation based testing of 450 patients suspected of having Prader-Willi syndrome. J Med Genet 32:88–92.

Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. 2001. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics 108:E92–E97.

Holland AJ, Treasure J, Coskeran P, Dallow J. 1995. Characteristics of the eating disorder in Prader-Willi syndrome: Implications for treatment. J Intellect Disabil Res 39:373–381.

Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. 2003. Postnatal growth in VLBW infants: Significant association with neurodevelopmental outcome. J Pediatr 143:163–170.

Lindgren AC, Hagenas L, Muller J, Blichfeldt S, Rosenborg M, Brismar T, Ritzen EM. 1998. Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favourably. Acta Paediatr 87:28–31.

Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S. 2000. Eating behavior in Prader-Willi syndrome, normal weight, and obese control groups. J Pediatr 137:50–55.

Lucas A. 1998. Programming by early nutrition: An experimental approach. J Nutr 128:401S–406S.

Malich S, Largo R, Schinzel A, Molinari L, Eiholzer U. 2000. Phenotypic heterogeneity of growth and psychometric intelligence in Prader-Willi syndrome: Variable expression of a contiguous gene syndrome or parent-child resemblance? Am J Med Genet 91:298–304.

Miller SP, Riley P, Shevell MI. 1999. The neonatal presentation of Prader-Willi syndrome revisited. J Pediatr 134:226–228.

Myers SE, Carrel AL, Whitman BY, Allen DB. 2000. Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility and growth in Prader-Willi syndrome. J Pediatr 137:42–49.

Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. 2007. Two years of growth hormone therapy in young children with Prader-Willi syndrome: Physical and neurodevelopmental benefits. Am J Med Genet Part A 143A:443–448.

Ong KK, Loos RJ. 2006. Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. Acta Paediatr 95:904–908.

Prader A, Labhart A, Willi H. 1956. Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr 86:1260–1261.

Prader A, Largo R, Molinari L, Issler C. 1989. Physical growth of Swiss children form birth to 20 years of age. Helv Paediatr Acta 43:1–125.

Schlumpf M, Eiholzer U, Gygax M, Schmid S, van dS I, l'Allemand D. 2006. A daily comprehensive muscle training programme increases lean mass and spontaneous activity in children with Prader-Willi syndrome after 6 months. J Pediatr Endocrinol Metab 19:65–74.

Schmidt H, Schwarz HP, Enders A. 2001. Dietary intervention in the first four years prevents abnormal weight gain but negatively affects height development in Prader-Willi syndrome. Acta Paediatr 90:468–469.

Skuse D, Pickles A, Wolke D, Reilly S. 1994. Postnatal growth and mental development: evidence for a "sensitive period". J Child Psychol Psychiatry 35:521–545.

Stadler DD. 1995. Nutritional management. In: Greenswag LR, Alexander R, editors. Management of Prader-Willi syndrome. New York: Springer. p 88–114.

Vogels A, Fryns JP. 2004. Age at diagnosis, body mass index and physical morbidity in children and adults with the Prader-Willi syndrome. Genet Couns 15:397–404.

Vogels A, Van Den EJ, Keymolen K, Mortier G, Devriendt K, Legius E, Fryns JP. 2004. Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. Eur J Hum Genet 12:238–240.

Whitman BY. 2003. Prader-Willi syndrome: A pervasive neurodevelopmental disorder requiring a multidisciplinary approach. In: Eiholzer U, l'Allemand D, Zipf W, editors. Prader-Willi syndrome as a model for obesity. Basel: Karger. p 200–210.

Whitman BY, Accardo P. 1987. Emotional symptoms in Prader Willi syndrome adolescents. Am J Med Genet 28:897–905.

Whitman B, Greenswag LR. 1995. Psychological and behavioural management. In: Greenswag LR, Alexander R, editors. Management of Prader Willi Syndrome. New York: Springer. p 125–141.

Whitman BY, Myers S, Carrel A, Allen D. 2002. The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: A 2-year, controlled study. Pediatrics 109:E35.

Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. 2001. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet 38:792–798.

Whittington J, Holland A, Webb T, Butler J, Clarke D, Boer H. 2002. Relationship between clinical and genetic diagnosis of Prader-Willi syndrome. J Med Genet 39:926–932.

Wigren M, Hansen S. 2003. Prader-Willi syndrome: Clinical picture, psychosocial support and current management. Child Care Health Dev 29:449–456.