Beneficial Effects of Growth Hormone Treatment on Cognition in Children with Prader-Willi Syndrome: A Randomized Controlled Trial and Longitudinal Study

Elbrich P. C. Siemensma, Roderick F. A. Tummers-de Lind van Wijngaarden, Dederieke A. M. Festen, Zyrhea C. E. Troeman, A. A. E. M. (Janielle) van Alfen-van der Velden, Barto J. Otten, Joost Rotteveel, Roelof J. H. Odink, G. C. B. (Karen) Bindels-de Heus, Mariette van Leeuwen, Danny A. J. P. Haring, Wilma Oostdijk, Gianni Bocca, E. C. A. Mieke Houdijk, A. S. Paul van Trotsenburg, J. J. Gera Hoorweg-Nijman, Hester van Wieringen, René C. F. M. Vreuls, Petr E. Jira, Eelco J. Schroor, Evelyn van Pinxteren-Nagler, Jan Willem Pilon, L. (Bert) Lunshof, and Anita C. S. Hokken-Koelega

Background: Knowledge about the effects of GH treatment on cognitive functioning in children with Prader-Willi syndrome (PWS) is limited.

Methods: Fifty prepubertal children aged 3.5 to 14 yr were studied in a randomized controlled GH trial during 2 yr, followed by a longitudinal study during 4 yr of GH treatment. Cognitive functioning was measured biennially by short forms of the WPPSI-R or WISC-R, depending on age. Total IQ (TIQ) score was estimated based on two subtest scores.

Results: During the randomized controlled trial, mean SD scores of all subtests and mean TIQ score remained similar compared to baseline in GH-treated children with PWS, whereas in untreated controls mean subtest SD scores and mean TIQ score decreased and became lower compared to baseline. This decline was significant for the Similarities ($P = 0.04$) and Vocabulary ($P = 0.03$) subtests. After 4 yr of GH treatment, mean SD scores on the Similarities and Block design subtests were significantly higher than at baseline ($P = 0.01$ and $P = 0.03$, respectively), and scores on Vocabulary and TIQ remained similar compared to baseline. At baseline, children with a maternal uniparental disomy had a significantly lower score on the Block design subtest ($P = 0.01$) but a larger increment on this subtest during 4 yr of GH treatment than children with a deletion. Lower baseline scores correlated significantly with higher increases in Similarities ($P = 0.04$) and Block design ($P < 0.0001$) SD scores.

Conclusions: Our study shows that GH treatment prevents deterioration of certain cognitive skills in children with PWS on the short term and significantly improves abstract reasoning and visuospatial skills during 4 yr of GH treatment. Furthermore, children with a greater deficit had more benefit from GH treatment. **(*J Clin Endocrinol Metab* 97: 2307–2314, 2012)**

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder resulting from the absence of expression of paternally expressed genes located on chromosome 15 at the locus q11-q13 caused by paternal deletion, maternal uniparental disomy (mUPD), imprinting errors, or paternal chromosomal translocation (1). PWS is characterized by a number of signs and symptoms, including muscular hypotonia, hypogonadism, short stature, obesity, psychomotor delay, neurobehavioral abnormalities, and cognitive impairment (2).

Long-term continuous GH treatment is an effective and safe treatment for children with PWS (3, 4). Previously, we showed that 1 yr of GH treatment significantly improved mental and motor development in infants with PWS, compared with randomized controls (5).

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*Author affiliations are shown at the bottom of next page.

Abbreviations: BMI, Body mass index; CI, confidence interval; ICD, imprinting center defect; mUPD, maternal uniparental disomy; PWS, Prader-Willi syndrome; RCT, randomized controlled trial; SDS, SD score; s-score, standard score.

There is little information about the effect of GH treatment on cognitive development in infants with PWS (5, 6) and no information about this effect in children with PWS above 3 yr of age beyond a period of 6 months. Studies in children born small for gestational age showed a significant increase in total IQ (TIQ) score during 9 yr of GH therapy, mainly due to increased scores in the performance area, compared with a Dutch reference population (7, 8). Recently, a study in adolescents with Down syndrome demonstrated a positive, although not significant, effect of GH treatment on cognitive function in 12 GH-treated patients compared with 10 controls 15 yr after its discontinuation. GH treatment was started at 7 yr of age and continued for 3 yr (9).

In our randomized controlled GH trial, we investigated the effect of GH treatment on cognitive functioning in children with PWS. Furthermore, we studied cognitive functioning during 4 yr of continuous GH treatment in the PWS cohort study and the effects of age at the start of GH treatment, serum IGF-I level, head circumference, and genotype on cognitive functioning. We hypothesized that long-term GH treatment has a positive effect on TIQ score and especially on performance, *i.e.* nonverbal abilities.

Patients and Methods

Patients

Fifty prepubertal children with PWS were included. All participants fulfilled the following inclusion criteria: 1) genetically confirmed diagnosis of PWS; 2) age between 3 and 12 yr (girls) or 14 yr (boys) at start of study; 3) bone age less than 14 yr (girls) or 16 yr (boys); and 4) prepubertal at start of study, defined as Tanner breast stage of 2 or less for girls and testicular volume less than 4 ml for boys (10). Children were regularly seen by a physiotherapist and speech therapist. The activity level of all children was standardized at 3 months before the start of the study. Compliance to exercise was evaluated by the research nurse in close collaboration with the physiotherapist and speech therapist.

Design

Randomized controlled trial (RCT)

In April 2002, a multicenter RCT was started in 50 children with PWS, investigating the effects of GH treatment *vs.* no GH treatment on growth, body composition, activity level, and psychosocial development. After stratification for age and body mass index (BMI), children were randomly assigned to either the GH treatment group or the control group for 2 yr.

Follow-up during 4 yr of continuous GH treatment

After the RCT, all children were treated with GH and followed in the Dutch PWS Cohort Study. To investigate the effect of long-term GH treatment on cognition, we analyzed their data from the start of GH treatment until after 4 yr of GH treatment. Children who had been in the control group of the RCT were on average 2 yr older at the start of GH treatment than those who had been in the treatment group of the RCT. Two children dropped out of the cohort study— one during the first year of GH treatment because of family problems, and the other during the third year of GH treatment because of very high IGF-I levels, even with a low GH dose. The data of these children were included in our analysis until they dropped out.

Biosynthetic GH (Genotropin; Pfizer Inc., New York, NY; dose, 1.0 mg/m^2/d) was administered sc once daily at bedtime in children of the treatment group during the RCT and in all children during the cohort study. All children were naive to GH treatment at the start of the RCT. During the entire study period, children were seen 3-monthly for anthropometric measurements by the PWS research team of the Dutch Growth Research Foundation, in collaboration with Dutch pediatric endocrinologists and pediatricians.

Cognitive functioning was measured biennially during the RCT and the follow-up during 4 yr of GH treatment. All cognitive measurements described in this study were performed in the Children's Hospital Erasmus MC-Sophia by one psychologist experienced in testing children with PWS. The psychologist was blinded for the randomization. Missing values occurred because children were tested by their school psychologist during the same period; this happened in a maximum of 14% of children at each time point.

The study protocol was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, The Netherlands. Written informed consent was obtained from the parents and from children older than 12 yr, and assent was obtained in children younger than 12 yr of age.

Anthropometry

At baseline and at 3-month intervals, anthropometric measurements were performed. Height was obtained using a Harpenden stadiometer. Weight was measured on an accurate scale. Height, weight, BMI, and head circumference were expressed as SD scores (SDS), adjusting for age and sex (11, 12). BMI and SDS of BMI, height, weight, and head circumference were calculated with Growthanalyser, version 3.0 (www.growthanalyser.org). A detailed description of anthropometric measurements was previously published (4).

Cognitive functioning

To assess intelligence, a short form of four subtests [Vocabulary, Similarities (verbal IQ subtests), Block design, and Picture arrangement (performance IQ subtests)] of the Wechsler Intel-

Dutch Growth Research Foundation (E.P.C.S., R.F.A.T.-d.L.v.W., D.A.M.F., Z.C.E.T., A.C.S.H.-K.), 3016 AH Rotterdam, The Netherlands; Departments of Pediatric Endocrinology, Erasmus University Medical Center Rotterdam/Sophia Children's Hospital (E.P.C.S., R.F.A.T.-d.L.v.W., D.A.M.F., G.C.B.B.-d.H., A.C.S.H.-K.), 3015 GJ Rotterdam, The Netherlands; Radboud University Nijmegen Medical Center (A.A.E.M.v.A.-v.d.V., B.J.O.), 6500 HB Nijmegen, The Netherlands; VU University Medical Center (J.R.), 1081 HV Amsterdam, The Netherlands; St. Catharina Hospital (R.J.H.O.), 5623 EJ Eindhoven, The Netherlands; St. Jansdal Hospital (M.v.L.), 3844 DG Harderwijk, The Netherlands; Diaconessen Hospital (D.A.J.P.H.), 2334 CK Leiden, The Netherlands; Leiden University Medical Center (W.O.), 2333 ZA Leiden, The Netherlands; University Medical Center Groningen/Beatrix Children's Hospital (G.B.), 9713 GZ Groningen, The Netherlands; Haga Hospitals/Juliana Children's Hospital (E.C.A.M.H.), 2566 MJ The Hague, The Netherlands; Academic Medical Center, University of Amsterdam (A.S.P.v.T.), 1105 AZ Amsterdam, The Netherlands; St. Antonius Hospital (J.J.G.H.-N., H.v.W.), 3430 EM Nieuwegein, The Netherlands; Medical Center Twente (R.C.F.M.V.), 7511 JX Enschede, The Netherlands; Department of Pediatrics, Jeroen Bosch Hospital (P.E.J.), 5200 ME 's-Hertogenbosch, The Netherlands; Isala Hospitals (E.J.S.), 8025 AB Zwolle, The Netherlands; Medical Center Leeuwarden (E.v.P.-N.), 8901 BR Leeuwarden, The Netherlands; IJsselmeer Hospitals (J.W.P.), 8233 AA Lelystad, The Netherlands; and Gelre Hospitals (L.L.), 7300 SD Apeldoorn, The Netherlands

ligence Scale for Children-Revised, Dutch version (WISC-R), was used in children over 7 yr of age (13). A short form of four subtests [Vocabulary, Similarities (verbal IQ subtests), Block design, and Picture completion (performance IQ subtests)] of the Wechsler Preschool and Primary Scale of Intelligence-Revised, Dutch version (WPPSI-R) was used for children younger than 7 yr of age (14, 15). We used short forms because of the short attention span in children with PWS.

Good correlations have been found between the short-form IQ and the full-scale IQ for both the WISC-R and the WIPPSI-R (16–18). Wechsler (19) showed that the WPPSI IQ and WISC IQ are comparable in 6-yr-old children. Three subtests—Vocabulary, Similarities, and Block design—were the same in the WISC-R and the WPPSI-R short forms. We therefore combined the results of these subtests to increase the sample size and corrected for a different type of test in our analyses.

Results of the Picture subtest of both WISC-R and WPPSI-R short forms had to be analyzed separately for each short form because this subtest differed between the WISC-R and the WPPSI-R (Picture arrangement in the WISC-R and Picture completion in the WPPSI-R short form). This resulted in too small numbers of patients per test, and we could therefore not analyze the scores on this subtest.

The scores on all subtests were expressed as SDS, based on normalized standard scores (s-scores) with a mean of 10, ranging from 1 (−3 SDS) to 19 (+3 SDS), based on Dutch population data for the same age (13, 15). TIQ score was calculated according to an equation based on Dutch outpatient population reference (TIQ = 45.3 + 2.91 × Vocabulary s-score + 2.50 × Block design s-score), as has been used in other studies (7, 8).

Assay

Serum IGF-I levels were measured in one central laboratory using a immunometric technique on an Advantage Automatic Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, CA). The intraassay coefficient of variation was 4%, and the interassay coefficient of variation was 6%. Because of age and sex dependency, IGF-I levels were transformed into SDS (20).

Data analysis

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL).

Independent samples *t* tests were used to compare the baseline characteristics between the GH-treated patients and the untreated controls.

To analyze the effect of GH treatment during the RCT and the longitudinal study, Linear Mixed Models (21) was used with GH treatment and time as factors (GH treatment coded as: 1 = GH-treatment group, and 0 = control group; time coded as: 1 = baseline; 2 = after 2 yr of study) in the RCT and time (time coded as: 1 = baseline, 2 = after 2 yr of GH treatment, 3 = after 4 yr of GH treatment) as the factor in the longitudinal study.

All subtest scores and TIQ scores were corrected for test type (WPPSI-R or WISC-R) age, gender, and genotype. The effects of age at the start of GH treatment, gender, genotype, serum IGF-I level, head circumference, and baseline scores on cognitive functioning during GH treatment were determined by using these variables as factors (in case of nominal or ordinal variables) or covariates (in case of scale variables) in the model.

TABLE 1. Baseline characteristics at start of the RCT

	GH-treated	Untreated controls	*P* value
n	29	21	
Age (yr)	7.4 [2.5]	6.4 [2.2]	0.165
Height SDS	−2.2 [1.4]	−2.4 [1.1]	0.540
Weight for height SDS	1.4 [1.3]	1.6 [1.0]	0.624
BMI SDS	1.2 [1.1]	1.4 [0.8]	0.439
Head circumference SDS	−0.7 [1.0]	−0.6 [0.8]	0.742
IGF-I SDS	−1.7 [1.1]	−1.9 [1.0]	0.504
Genetic cause			
Deletion	13	7	
UPD	9	10	
ICD	1	1	
Unknown	3	3	

Data are expressed as mean [SD]. UPD, Uniparental disomy.

Results

Randomized controlled trial

Baseline characteristics

Fifty prepubertal children with PWS (21 boys, 29 girls) were included (Table 1). At the start of the RCT, the mean (SD) age was 7.4 (2.5) yr in the treatment group and 6.4 (2.2) yr in the control group ($P = 0.2$). Children had a baseline height and head circumference significantly below 0 SDS ($P < 0.0001$ for both) and low IGF-I levels. Twenty children (40%) had a deletion of chromosome 15q11-q13, 19 (38%) had a mUPD, and five (10%) had an imprinting center defect (ICD). Positive methylation test was demonstrated in the remaining six (12%) patients, but the underlying genetic defect was not identified. There were no significant differences between the treated and untreated controls at baseline.

Effect of GH treatment vs. *no treatment on cognitive functioning*

Figure 1 shows the mean subtest scores and mean TIQ score at baseline and after 2 yr of study of GH-treated *vs.* randomized controls with PWS. At baseline, there were no significant differences in subtest SDS and TIQ scores between the treatment group and the controls.

After 2 yr of study, mean SDS on all subtests and mean TIQ score remained similar compared with baseline in GH-treated children with PWS, indicating that the development of cognitive functioning and TIQ score of GH-treated children with PWS, measured by Similarities, Block design, and Vocabulary subtests, took place at a similar pace as in healthy references. In untreated controls, however, mean subtest SDS and TIQ score were lower compared with baseline after 2 yr of study. This decrease was significant for the Similarities and Vocabulary subtests [mean difference (95% confidence interval; CI) between baseline and after 2 yr of study, −0.7 (−1.3 to 0.03)

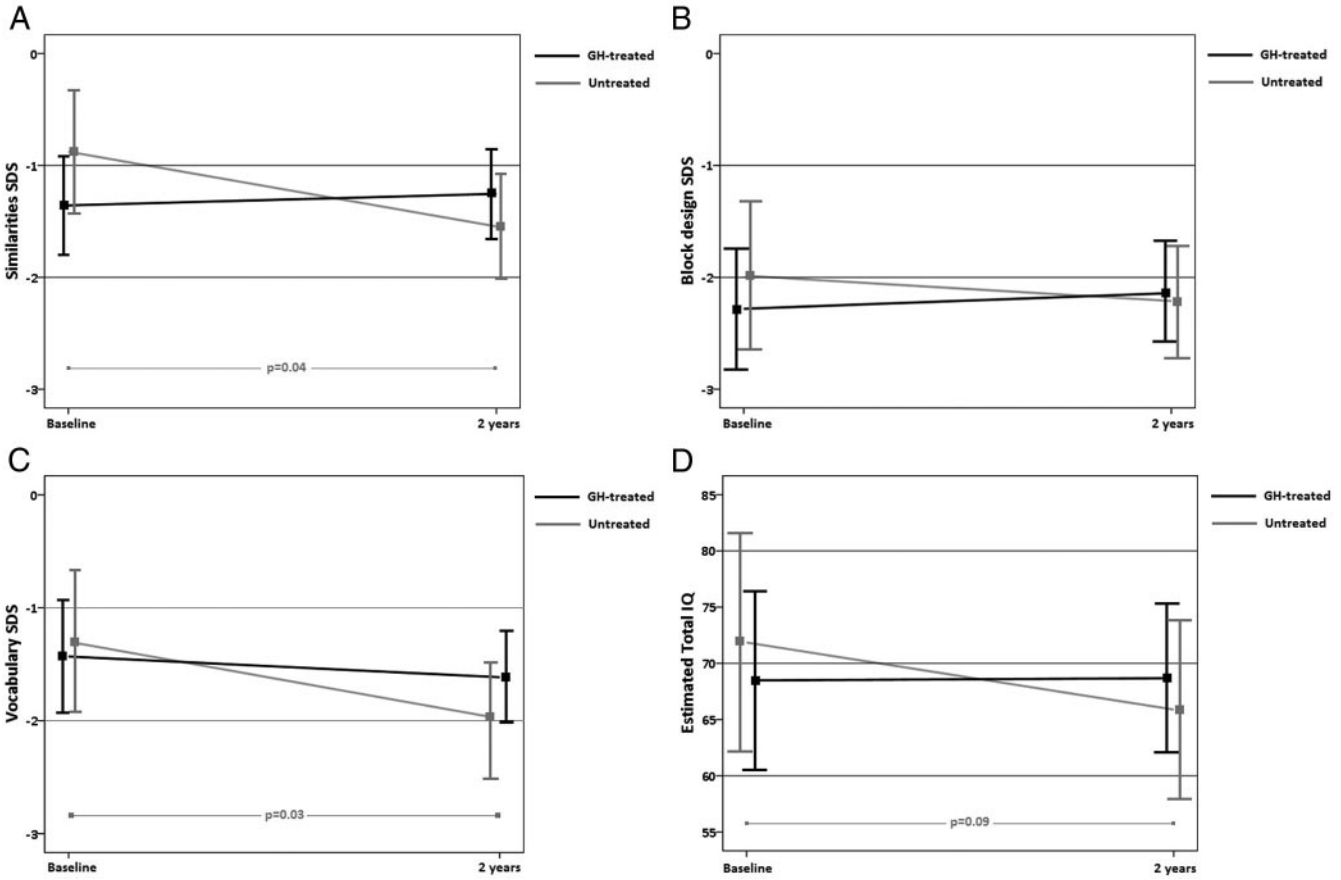

FIG. 1. Subtest scores and TIQ score during RCT in GH-treated and untreated children with PWS. This figure shows the mean SDS on the subtests Similarities (A), Block design (B), and Vocabulary (C), the TIQ score (D), and their 95% CI at baseline and after 2 yr of study in GH-treated children with PWS (*black lines*) and untreated controls (*gray lines*). *P* values of differences between baseline and after 2 yr of study in the untreated controls are indicated in *gray*.

SDS, $P = 0.04$ for Similarities; and −0.7 (−1.3 to 0.07) SDS; $P = 0.03$ for Vocabulary]. Thus, in untreated controls, there was a significant deterioration of certain cognitive skills and a nonsignificant deterioration of TIQ compared with healthy references.

After 2 yr of study, we found no significant differences between the subtest scores and TIQ scores of the GH-treated children and the control group, probably due to the large variation in subtest scores and TIQ scores within each group.

Long-term GH treatment

Fifty prepubertal children, originally included in the RCT, were followed during 4 yr of continuous GH treatment. Their mean (SD) age at the start of GH treatment was 7.8 (2.4) yr.

Cognitive functioning during long-term GH treatment

Figure 2 shows the longitudinal data during 4 yr of GH treatment. After 4 yr of GH treatment, mean SDS on the Similarities and Block design subtests were significantly higher than at baseline [mean difference (95% CI) between baseline and after 4 yr of GH treatment, +0.4 (−0.1 to 0.7) SDS, $P = 0.01$ for Similarities; and +0.3 (0.07 to 0.6) SDS, $P = 0.01$, for Block design], indicating that long-term GH treatment had significantly improved abstract verbal reasoning (Similarities subtest) and visuospatial skills (Block design subtest) and had reduced the gap between children with PWS and healthy controls on these skills.

Mean SDS on the Vocabulary subtest remained unchanged. Thus, during long-term GH treatment, children with PWS developed their vocabulary at the same pace as healthy references. Mean estimated TIQ score improved 4 points during 4 yr of GH treatment. This improvement did not reach significance ($P = 0.2$), probably due to the large variation in TIQ scores in children with PWS.

Influence of clinical and genetic characteristics on cognitive functioning

At baseline, we found significant effects of age at the start of GH treatment and head circumference SDS on Block design and Vocabulary SDS and estimated TIQ

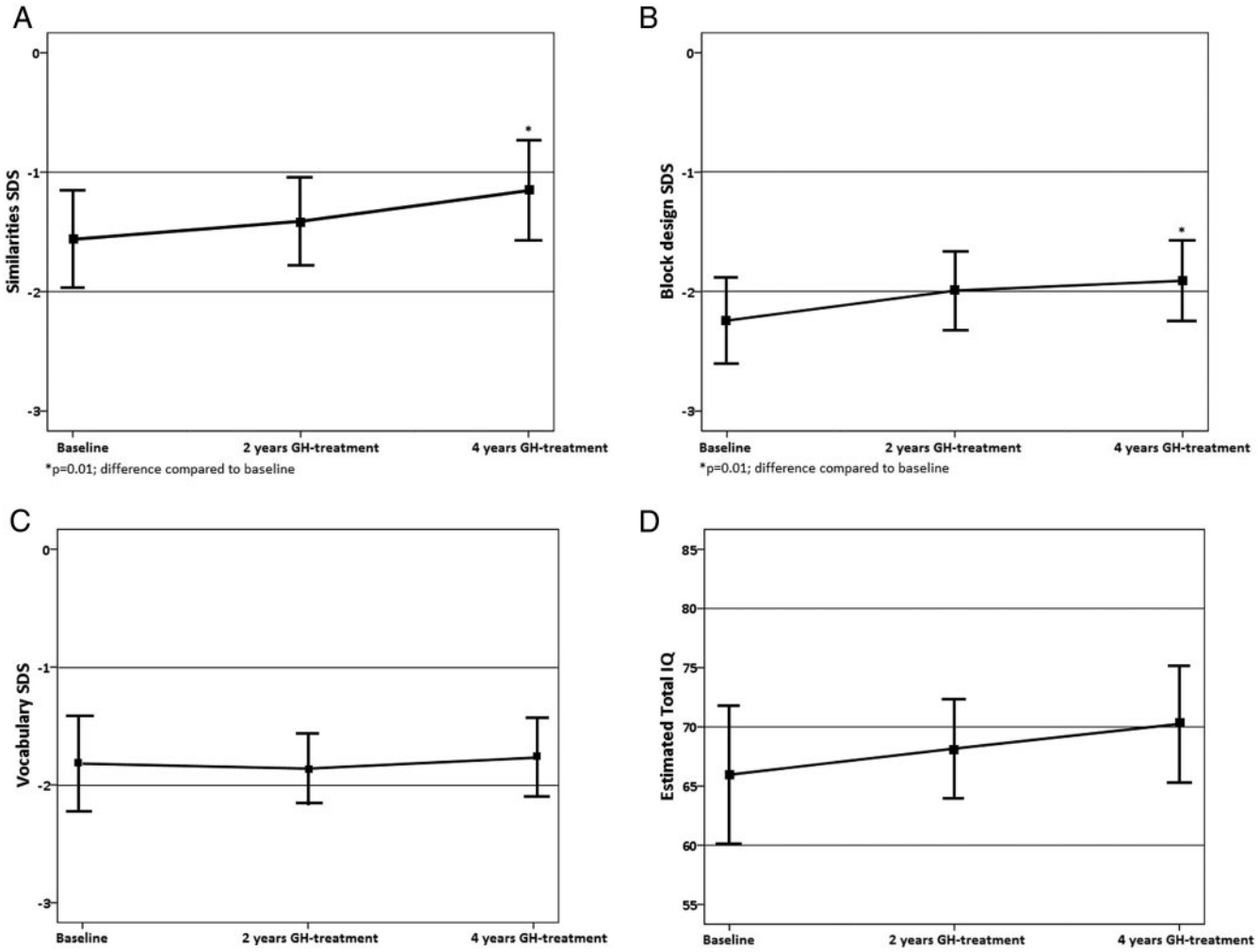

FIG. 2. Cognitive development during 4 yr of continuous GH treatment. This figure shows the mean SDS on the subtests Similarities (A), Block design (B), and Vocabulary (C), and the TIQ score (D) and their 95% CI during 4 yr of continuous GH treatment in children with PWS. Significant *P* values of differences between baseline and after 4 yr of GH treatment are indicated. Scores are the mean subtest scores and TIQ score of all children at the start of GH treatment. Thus, for children in the treatment group of the RCT, these are the subtest scores and TIQ score at the start of the RCT, and for children in the untreated control group these are the subtest scores and TIQ score at the end of the RCT.

score. The younger the children were at baseline, the higher they scored on these subtests and the higher their TIQ scores ($P = 0.006$, $P = 0.02$, and $P = 0.005$ for Block design SDS, Vocabulary SDS, and TIQ scores, respectively). We found a comparable effect of age on Similarities SDS, but this did not reach significance ($P = 0.08$). Children with a smaller head circumference SDS scored significantly lower on Block design and Vocabulary subtests, and they had significantly lower estimated TIQ scores than children who had a head circumference in the normal range compared with Dutch references ($P = 0.03$, $P = 0.04$, and $P = 0.02$ for Block design, Vocabulary, and TIQ scores, respectively). After 4 yr of GH treatment, the associations of age and head circumference SDS with cognitive outcomes were no longer significant.

Genotype had a significant effect on Block design SDS at baseline, and also after correction for age at the start of GH treatment and head circumference SDS. Scores were significantly lower in children with an mUPD than in children with a deletion genotype ($P = 0.01$). During 4 yr of GH treatment, children with mUPD showed a significant catch-up on the Block design subtest score compared with baseline ($P = 0.05$), and after 4 yr, the difference between deletion and mUPD genotype was no longer significant (Fig. 3). Children with an ICD genotype showed a comparable pattern as children with mUPD, but the differences were not significant due to the small number of children with an ICD. We found no effects of genotype on the other subtests or TIQ score.

There were no significant effects of serum IGF-I levels, height, weight, BMI, and gender on any subtest scores or TIQ score, either at baseline or after 4 yr of GH treatment.

Influence of baseline scores on cognitive functioning

We found a significant effect of baseline SDS on the changes in Similarities and Block design subtest scores

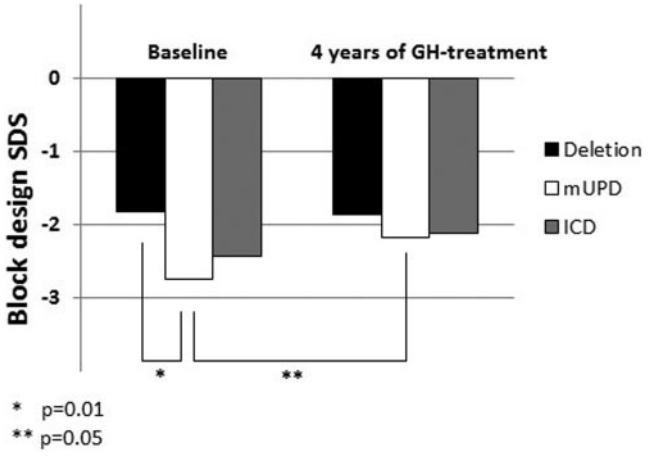

FIG. 3. Block design SDS per genotype at baseline and after 4 yr of GH treatment. This figure shows the mean SDS at baseline and after 4 yr of continuous GH treatment on the Block design subtest for children with deletion, mUPD, and ICD separately. The significant *P* values of the differences between the scores of children with different genotypes and between scores at baseline and after 4 yr of GH treatment are indicated.

from baseline to 4 yr of GH treatment. Children with the lowest scores at baseline showed the highest catch-up in SDS ($P = 0.04$ and $P < 0.0001$ for Similarities and Block design, respectively).

After correction for baseline scores, we found no effect of age at the start of GH treatment, gender, genotype, Δ head circumference (0–4 yr), and Δ IGF-I (0–4 yr) on the change in subtest and TIQ scores.

Discussion

Our study is the first to describe the effect of GH treatment on cognitive functioning in children with PWS during a 2-yr randomized controlled trial and during GH treatment for 4 yr. Our results demonstrate that GH treatment prevents deterioration of certain cognitive skills on the short term and significantly improves abstract verbal reasoning and visuospatial skills during 4 yr of GH treatment. Children with an mUPD started off with significantly lower visuospatial skills but showed a larger improvement on these skills after 4 yr of GH treatment than children with a deletion genotype. Furthermore, in children with lower cognitive functioning at baseline, GH treatment had a greater effect on abstract verbal reasoning and visuospatial skills.

There is only one other study reporting the effect of GH treatment on cognition in children (age > 3 yr) with PWS (22). The authors could not find an effect, but this might be due to their small patient number (n = 12) and short period of GH treatment (6 months). Studies in infants and adults with PWS did show an effect of GH treatment on cognition (5, 6, 23), as did studies in children with GH deficiency (24), children born small for gestational age (7, 8), and children with Down syndrome (9).

Our findings show that GH treatment improves abstract verbal reasoning and visuospatial skills in children with PWS. This is in line with other studies showing that GH treatment can influence spatial skills. In GH-deficient adults, GH treatment prevented spatial memory impairment (25), and in hypophysectomized rats, spatial performance was significantly better in GH-treated than in untreated animals (26).

It is known that GH receptors are located throughout the brain and that GH and IGF-I affect the genesis of neurons, astrocytes, endothelial cells, and oligodendrocytes (27). Recently, GH treatment has been shown to induce cell genesis in the adult brain (28). Furthermore, GH increases connexin-43 expression (a ubiquitous biochemical marker for gap-junction formation in the brain) in the cerebral cortex and the hypothalamus, thereby enhancing cell to cell communication in the central nervous system (29). We found no relation between cognitive functioning and IGF-I levels, and as far as we know, such a relationship has not been found in other studies regarding the effect of GH treatment on cognitive functioning in children. This suggests that the effect of GH on cognitive functioning in PWS might be paracrine in the brain. It has indeed been shown that GH has many effects in the central nervous system that are independent of serum IGF-I levels (30–32). The effects of GH treatment we demonstrated in our RCT and long-term study in children with PWS, in combination with the findings listed above, indicate plasticity of the human brain and the local activity of GH and IGF-I.

Another explanation for the improved cognitive skills during GH treatment could be that there is a relation with sleep-related breathing disorders in children with PWS. A few years ago, we studied sleep-related breathing during GH treatment in children with PWS (33) and found a nonsignificant decrease of the Apnea Hypopnea index after 6 months of GH treatment. However, because we did not find any significant relation between cognition and the central or obstructive apnea index in untreated children with PWS in another study (34), it seems unlikely that the improved cognitive performance is the result of less sleep-related breathing disorders.

Before the start of GH treatment, older age had a significant negative effect on cognition. Also, untreated controls showed a deterioration of cognitive functioning. These findings indicate that cognitive functioning of untreated children with PWS deteriorates over time compared with healthy children. Our study shows that GH treatment prevents this deterioration. As a result, the relation between age and cognition was no longer significant after 4 yr of GH treatment. In addition, we

found that baseline scores had a significant effect on the change in scores on the Similarities and Block design subtests during GH treatment. It appeared that GH treatment was most beneficial for children with the lowest scores. Baseline scores were even more important for the degree of catch-up in cognitive skills than age at the start of GH treatment, gender, genotype, Δ head circumference, or Δ IGF-I. Our findings might suggest that GH should best be administered at an early age to prevent deterioration of cognitive functioning in children with PWS, but that GH treatment also induces a catch-up in cognitive skills in children with PWS who lag behind, even when they start at an older age.

Before the start of GH treatment, children with a deletion genotype scored better on the Block design subtest than children with mUPD. Comparable differences between genetic subtypes of PWS have been noted in other studies. The deletion genotype is associated with better performance IQ scores and the mUPD genotype with better verbal IQ scores (35). A recent study investigated dorsal and ventral stream-mediated visual processing in PWS (36). They found that children with a deletion genotype, but not children with an mUPD genotype, had a relative strength in visual processing in the ventral stream. This might explain the difference in baseline Block design test scores between the children with a deletion and those with mUPD.

In most studies, patients with PWS are described as having a mild-to-moderate learning disability with a TIQ score below 70 (23, 35). At baseline, the majority of the children in our study had indeed a TIQ score below 70, comparable to what is found in other studies. During long-term GH treatment, the mean TIQ score increased, although not significantly, from 66 at baseline to 70 after 4 yr of GH treatment, meaning that at this point only half of the children with PWS in our study will be diagnosed mentally retarded according to the DSM-IV. In another study investigating the effects of GH treatment on cognition in children born small for gestational age after 2 and 8 yr, authors found a significant increase of 0.7 SDS on the Block Design subtest and of 7 points on TIQ score over a period of 8 yr of GH treatment (8). After 2 yr, there was already a positive but nonsignificant effect of GH treatment on cognition, which increased in the subsequent 6 yr to the significant improvement at 8 yr after the start of GH treatment.

These and our data might suggest that the improvement of cognitive functioning during GH treatment becomes larger over time. As a result, the clinical effects become clearer with longer duration of GH treatment, especially if one keeps in mind that untreated children with PWS have a deterioration of cognitive functioning as shown in the RCT. The effects of GH treatment on cognitive skills in children with PWS would probably have been more significant if we could have studied a much larger group. However, PWS is a rare disorder, and in the present study we evaluated a relatively large group of children with PWS.

Next to the increase in TIQ score, parents did not report an increase in behavioral problems or food seeking behavior during GH treatment. They rather reported a decrease in problem behavior, but this needs further investigation.

Mean subtest scores on all subtests, except Block design, were in the normal range compared with healthy children (higher than −2 SDS) during the entire long-term study. The mean score on Block design was below −2 SDS at baseline, but after 4 yr of GH treatment, the mean score on Block design SDS was also in the normal range. This points out that the increase in TIQ score was mostly due to the increase on Block design score, a performance test.

Our study shows that GH treatment prevents deterioration of certain cognitive skills in children with PWS in the short term and significantly improves abstract verbal reasoning and visuospatial skills during 4 yr of GH treatment compared with a reference population. The more children lag behind, the more they benefit from GH treatment. Based on our results, we conclude that GH treatment in children with PWS is not merely an effective treatment for normalizing height and improving body composition, but it also has a beneficial effect on their cognitive functioning.

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Address all correspondence and requests for reprints to: Elbrich P. C. Siemensma, M.D., Dutch Growth Research Foundation/Erasmus MC Rotterdam, Westzeedijk 106, 3016 AH Rotterdam, The Netherlands. E-mail: e.siemensma@kindengroei.nl.

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