Growth Hormone Therapy, Muscle Thickness, and Motor Development in Prader-Willi Syndrome: An RCT

AUTHORS: Linda Reus, PhD,a,b Sigrid Pillen, MD, PhD,c Jan J. Pelzer, PhD,c Janielle A.A.E.M. van Alffen-van der Velden, MD, PhD,d Anita C.S. Hokken-Koelega, MD, PhD,e Machiel Zwarts, MD, PhD,h Barto J. Otten, MD, PhD,c and Maria W.G. Nijhuis-van der Sanden, PT, PhD,a,b

aDepartment of Rehabilitation, Pediatric Physical Therapy, bScientific Institute for Quality of Healthcare, cFaculty of Social Sciences, and dDepartment of Pediatric Endocrinology, Radboud University Medical Center, Nijmegen, Netherlands; eChild Development and Exercise Center, Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, Netherlands; fDutch Growth Research Foundation, Rotterdam, Netherlands; gDepartment of Pediatric Endocrinology, Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands; and hKempenhaeghe, Epilepsy Centre, Heeze, Netherlands

KEY WORDS
body composition, growth hormone, infants, motor development, muscle development, Prader-Willi syndrome

ABBREVIATIONS
GH—growth hormone
GMFM—Gross Motor Function Measurement
IMS—Infant Muscle Strength
LBM—lean body mass
MLRA—multilevel regression analysis
PWS—Prader-Willi syndrome

Ms Reus and Dr Pillen contributed to the conception and design of the study, the acquisition, analyses, and interpretation of the data; and the drafting of the manuscript. Drs van Alffen-van der Velden, Hokken-Koelega, and Zwarts contributed to the drafting and revision of the manuscript. Dr Pelzer contributed to the analyses, interpretation of data, and the drafting and critical revision of the manuscript; Drs Nijhuis-van der Sanden and Otten contributed to the conception and design of the study, analysis and interpretation of data, and drafting and critical revision of the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Linda Reus, MSc, Department of Rehabilitation, Pediatric Physical Therapy 818, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: lin.reus@gmail.com

WHAT’S KNOWN ON THIS SUBJECT: Infants with Prader-Willi syndrome suffer from hypotonia, muscle weakness, and motor developmental delay and have increased fat mass combined with decreased muscle mass. Growth hormone improves body composition and motor development.

WHAT THIS STUDY ADDS: Ultrasound scans confirmed decreased muscle thickness in infants with Prader-Willi syndrome, which improved as result of growth hormone treatment. Muscle thickness was correlated to muscle strength and motor performance. Catch-up growth in muscle thickness was related to muscle use independent of growth hormone.

abstract

OBJECTIVE: To investigate the effect of physical training combined with growth hormone (GH) on muscle thickness and its relationship with muscle strength and motor development in infants with Prader-Willi syndrome (PWS).

METHODS: In a randomized controlled trial, 22 infants with PWS (12.9 ± 7.1 months) were followed over 2 years to compare a treatment group (n = 10) with a waiting-list control group (n = 12). Muscle thickness of 4 muscle groups was measured by using ultrasound. Muscle strength was evaluated by using the Infant Muscle Strength meter. Motor performance was measured with the Gross Motor Function Measurement. Analyses of variance were used to evaluate between-group effects of GH on muscle thickness at 6 months and to compare pre- and posttreatment (after 12 months of GH) values. Multilevel analyses were used to evaluate effects of GH on muscle thickness over time, and multilevel bivariate analyses were used to test relationships between muscle thickness, muscle strength, and motor performance.

RESULTS: A significant positive effect of GH on muscle thickness (P < .05) was found. Positive relationships were found between muscle thickness and muscle strength (r = 0.61, P < .001), muscle thickness and motor performance (r = 0.81, P < .001), and muscle strength and motor performance (r = 0.76, P < .001).

CONCLUSIONS: GH increased muscle thickness, which was related to muscle strength and motor development in infants with PWS. Catch-up growth was faster in muscles that are most frequently used in early development. Because this effect was independent of GH, it suggests a training effect. Pediatrics 2014;134:e1619–e1627
Prader-Willi syndrome (PWS) is a multisystem disorder with an estimated prevalence of 1 in 10,000 to 30,000 live births. The syndrome results from lack of expression of the paternally derived chromosome 15q11-q13, caused by a deletion, uniparental disomy, an imprinting center defect, or balanced translocations. PWS is characterized by hypotonia, short stature, hyperphagia, obesity, mild dysmorphic facial features, cognitive and behavioral deficits, and by endocrine disturbances such as hypogonadism and growth hormone (GH) deficiency. In infancy, severe hypotonia combined with muscle weakness leads to serious motor developmental delay. These motor problems persist, although they are less marked, in childhood and adulthood. It is presumed that the motor problems are related to an increased fat:muscle ratio even in underweight infants with PWS. In infants with PWS, body fat percentages range from 28% to 32%, increasing to 36% to 55% during childhood; in developmentally normal infants, this percentage is 24%, decreasing to 18% during childhood. In children and infants with PWS, body fat percentages decrease as a result of GH treatment, although the fat:muscle ratio does not normalize. Dual-energy radiograph absorptiometry revealed a positive GH effect on lean body mass (LBM), which mainly contains muscle tissue. In infants with PWS, GH positively influences motor development. In children with PWS, GH treatment has a positive effect on agility and thoracic muscle strength. To relate decreased muscle thickness in PWS to muscle weakness and motor developmental delay, it would be interesting to use a more direct measure of specific muscle groups and compare this with strength measurement to determine the direct relationship between structure and function. We hypothesize that GH improves muscle strength and motor development by increasing muscle mass in infants with PWS. This is the first time, to our knowledge, that muscle thickness measurement with ultrasound was combined with strength measurement in specific muscle groups, with the use of a longitudinal design with frequent measurements focusing on the additional effect of GH on training, to gain more understanding of the relation between muscle thickness, muscle strength, and motor development in infants with PWS.

METHODS

Design

This study was part of a 2-year randomized, single-blind controlled trial focused on motor development in infants with PWS at the Radboud University Medical Center. All infants received physical training and were randomly assigned (1:1) either to the GH group, in which infants were treated with 1 mg/m² per day GH (Genotropin; Pfizer, New York, NY), or to a control group, in which GH treatment started after an initial control period (see Fig 1). Randomization was performed by the Dutch Growth Research Foundation by using a computer-generated list of random numbers. Originally we planned a control period of 12 months; however, the results of Festen et al. revealed the effectiveness of GH, so we shortened the control period to 6 months on ethical grounds. An extra measurement 3 months after baseline was added to provide 3 measurements in the control condition (Fig 1). During the 2-year study period, muscle ultrasound measurements were taken at 6-month intervals, and muscle strength and motor performance were assessed at 3-month intervals. The study leader (M.W.G.N.-v.d.S.), researcher (L.R.), the electrodiagnostic technicians performing the muscle ultrasound scans (H.Janssen, W.Raijmann, and J.Bor), and the pediatric physical therapists (A.Zweers and I.Durein) were all blinded to the group assignment of subjects. All parents gave written informed consent, and the study was approved by the Medical Ethics Committees of the Erasmus Medical Centre Rotterdam and Radboud University Medical Center.

Participants

All parents of infants with PWS up to the age of 36 months who were registered at the Dutch Growth Research Foundation between September 2006 and June 2010 (the majority of infants with PWS in The Netherlands diagnosed within that period) were invited to participate. The patient recruitment procedure has been previously reported. Of 27 potential participants, parents of 2 of the infants did not want to participate, 3 infants were excluded, and parents of 2 infants refused GH treatment but wanted to participate in the training; these infants were added to the control group without randomization. Hence, 20 infants were randomly assigned as follows: 10 to the GH group and 10 to the control group, giving final group sizes of GH = 10 and control = 12 (Fig 1 and Reus et al 2013). The mean ± SD age at the start of study was 12.9 ± 7.1 months (range: 4.7–31.8 months), and the mean ± SD age at the start of GH treatment was 17.5 ± 7.3 months (range: 6.7–34.2 months). The clinical characteristics of the subjects and genetic subtypes are presented in Table 1.

Outcome Measures

Muscle Measurement

Muscle thickness and muscle echo intensity of the left biceps brachii, right forearm flexors, right quadriceps, and left tibialis anterior muscle were measured by using ultrasound. This technique shows high reliability and reproducibility in measuring muscle thickness when compared with MRI. The measurements were performed by 3 well-trained electrodiagnostic technicians (H.Janssen, W.Raijmann, and J.Bor) by using an IU22 ultrasound device (Philips, Best, The Netherlands) with a linear broadband with a 17 to 5 MHz extended operating
frequency range. Measurements were made at fixed, anatomically defined positions as described in a previous study. Because muscle thickness is especially related to body mass, and $z$ scores are corrected for weight, all muscle thickness and muscle echo intensity data were expressed as $z$ scores (ie, the number of SDs above or below normal) compared with weight-specific reference values. Echo intensity scores were considered abnormal if the $z$ score exceeded 3.5 SDs in 1 muscle group, 2.5 SDs in 2 muscle groups, or 1.5 SDs in 3 muscle groups. The $z$ scores for each muscle group and an overall average muscle thickness score (sum of absolute muscle thickness score per muscle group divided by 4) were used as outcome measures.

### Muscle Strength and Motor Performance

Muscle strength was measured in the same muscle group as measured by the ultrasound: the biceps brachii and forearm flexors using a pulling task to evoke maximal pulling activity. Because there were no methods to objectify muscle strength in young infants, our research group developed such a method: the Infant Muscle Strength (IMS) meter. The IMS meter was found to be a reliable and valid measurement method for measuring muscle strength objectively in infants from 6 to 36 months, and it was also tested.

<table>
<thead>
<tr>
<th>TABLE 1 Clinical Characteristics at Baseline for All Infants</th>
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<tbody>
<tr>
<td>All Subjects ($N = 22$)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Gender (M/F), $n$</td>
</tr>
<tr>
<td>Ethnicity (Dutch/non-Dutch), $n$</td>
</tr>
<tr>
<td>Genetic subtype (deletion/UPD/unknown), $n$</td>
</tr>
<tr>
<td>Age, mean (SD), mo</td>
</tr>
<tr>
<td>Height, mean (SD), SDS</td>
</tr>
<tr>
<td>Weight, mean (SD), SDS</td>
</tr>
<tr>
<td>Muscle thickness, mean (SD), SDS</td>
</tr>
<tr>
<td>Biceps brachii</td>
</tr>
<tr>
<td>Forearm flexors</td>
</tr>
<tr>
<td>Quadriceps</td>
</tr>
<tr>
<td>Tibialis anterior</td>
</tr>
<tr>
<td>Muscle strength, $r$ mean (SD)</td>
</tr>
<tr>
<td>IMS, N</td>
</tr>
<tr>
<td>IMS% $c$</td>
</tr>
<tr>
<td>Motor performance, mean (SD)</td>
</tr>
<tr>
<td>GMFM total score</td>
</tr>
</tbody>
</table>

$a$ SDS significantly below 0, $P \leq .001$. SDS, SD score; UPD, uniparental maternal disomy.

$^b$ All infants were born in The Netherlands, but 3 families came from the Middle East.

$^c$ Muscle strength could not be measured in all infants at baseline, because at the start of the study not all infants were able to perform the pulling task used to measure muscle strength because of motor developmental delay. We have therefore reported the results of the first measurement made at a mean age of 17.2 (±7.0) months, which is, in most infants, the first or second measurement of the trial.

$^d$ IMS% = (observed IMS/predicted IMS) × 100.
in 24-month-old infants with PWS. Muscle strength can be assessed from the moment the infant is able to sit with support and reach and grasp an object, typically from 6 months of age. The percentage of IMS (IMS%) was calculated by using reference data from a prediction model by dividing observed IMS by predicted IMS (on the basis of age, height, and weight). Both IMS and IMS% were used as outcome measurements.

Motor performance was assessed by using the Gross Motor Function Measure (GMFM). This test contains 88 items grouped into 5 dimensions (eg, lying and rolling, sitting, crawling and kneeling, standing, walking, running and jumping) and is sensitive to motor developmental changes over time in infants with PWS in whom motor development is seriously delayed. Typically developing children can perform correctly on all 88 items at the age of 5 years. Each item is scored on a 4-point ordinal scale, and a percentage total GMFM score was calculated by dividing the sum of the actual item scores by the possible maximum score. This score was used as an outcome measure. All assessments of muscle strength and motor performance were performed by 2 well-trained pediatric physiotherapists (AZweers and IDurein).

Statistical Analyses
Descriptive statistics were used to characterize and compare the groups at baseline. A binomial test was used to compare z scores in infants with PWS with developmental norms with respect to height, weight, and muscle thickness. Analysis of variance was used to compare muscle thickness z scores between groups after 6 months (GH versus control) and to compare pretreatment scores with scores after 12 months of GH treatment (both groups). Multilevel regression analyses (MLRAs) were used to evaluate muscle thickness z scores over time, taking both within-subject variance (level 1) and between-subject variance (level 2) into account. This technique is well suited to the analysis of data related to growth. For each muscle group, a regression model was developed to predict muscle growth by using age, baseline muscle thickness, and GH as explanatory variables. We tested model fit by calculating the proportional reduction in unexplained variance between a model with no explanatory variables (empty model) and the final models. Multilevel bivariate analyses were used to calculate interclass correlations between the average muscle thickness of 4 muscle groups, muscle strength (as IMS score), and motor performance (as GMFM score). MLRA was performed by using “lmer” in the software package R (R Project for Statistical Computing, Vienna, Austria); other statistical analyses were performed using SPSS 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS
Baseline Results
The groups did not differ in terms of clinical characteristics at baseline (Table 1). Height, weight, and muscle thickness of biceps brachii, forearm flexors, quadriceps, and tibialis anterior, all expressed as SD scores, were significantly lower than in healthy peers. All muscle echo intensity measurements were normal. Muscle strength was 58% of predicted muscle strength for healthy peers corrected for age, height, and weight, which is comparable to previously reported motor developmental outcomes in PWS (55% of normal reference).

Muscle Ultrasound Results
After 6 months, the forearm flexors were significantly thicker in the GH group than the in the control group (Table 2). Furthermore, after 12 months, muscle thickness in the GH group had improved significantly in the biceps brachii, forearm flexors, and tibialis anterior compared with baseline, whereas in the control group only the muscle thickness of the tibialis anterior had improved (Table 2).

After 12 months of GH treatment, muscle thickness in the forearm flexors and quadriceps was significantly improved in both groups, and thickness of the biceps brachii and tibialis anterior muscles had increased in the GH group (Table 2).

Development of Muscle Thickness (MLRA models)
We also evaluated the effect of GH over time by using MLRA. For each muscle, 118 muscle ultrasound scans were analyzed; in 8 infants 5 repeated scans were available and in 14 infants 6 repeated scans were available (124 − 6 missing) of which 52 were control observations. Models for all 4 muscle groups showed a significant positive effect of GH on muscle thickness when controlled for age and baseline muscle thickness (Table 3, Fig 2). The models

| TABLE 2 SD Scores of Muscle Thickness in Control and GH Groups at Baseline, at 6 Months (GH Versus Control), and After 12 Months of GH Treatment in Both Groups |
|-----------------|-----------------|-----------------|-----------------|
|                 | Baseline        | T2 (Control or GH at 6 Months) | GH 12 Months (Both Groups After 12 Months of GH) |
|                 | Control         | GH              | Control         | GH              |
| Biceps brachii  | −1.5 (0.7)      | −1.7 (0.7)      | −1.4 (0.8)      | −0.5 (1.7)      | −0.7 (0.9)      | −0.6 (1.0)      |
| Forearm flexors | −1.2 (0.9)      | −1.3 (1.1)      | −1.3 (0.8)      | −0.5 (0.9)      | −0.3 (0.6)      | −0.1 (1.0)      |
| Quadriceps      | −1.8 (1.0)      | −1.5 (0.9)      | −1.4 (0.9)      | −0.9 (1.4)      | −0.4 (0.7)      | −0.5 (1.0)      |
| Tibialis anterior| −1.5 (0.5)      | −1.8 (0.5)      | −0.8 (0.6)      | −0.6 (1.1)      | −0.8 (1.1)      | −0.8 (0.9)      |

Data are presented as mean (SD).

* Baseline versus T2, P < .05.
* Pretreatment versus 12-month GH, P < .05. In the GH group, pretreatment is baseline; in the control group, pretreatment is the final observation of the control period.
* Between-group difference, P < .05.
predicted the same effect independent of the age at which GH treatment started. In the biceps brachii and tibialis anterior models, muscle thickness did not change over time (no age effect), indicating that growth rate was similar to typical development, although GH treatment enhanced the effect on muscle thickness (Table 3, Fig 2 A and D). In the quadriceps and forearm flexor models, muscle thickness improved (a significant positive age effect; Table 3, Fig 2 B and C), indicating that growth rate was increased compared with typical development, and GH accelerated the process of catching up by increasing muscle thickness. Moreover, a significant effect of baseline in all 4 models suggested that differences in muscle thickness between subjects were at least partly determined by individual differences at baseline (Table 3). This baseline effect varied between muscle groups: the biceps brachii and tibialis anterior were initially thicker and remained consistently thicker over time; the forearm flexors and quadriceps muscles showed a faster growth rate in infants with initially smaller muscles (significant negative interaction effect; Table 3), indicating catch-up over time, particularly in infants who had thinner muscles at baseline.

Assessing the fit of the model for muscle development by comparison with observed data revealed that proportional reduction in unexplained variance varied between 57% and 78%, which indicated a moderate to good fit (Table 3).

**Relationship Between Muscle Thickness, Muscle Strength, and Motor Performance**

Twenty-five infants had not yet mastered the required pulling skills at the start of the study and 5 refused to perform the test, so 88 IMS measurements were available for analysis. One GMFM measurement was missing, so 117 GMFM measurements were available for comparative analysis. IMS and GMFM were measured every 3 months, so 154 simultaneous observations were made, 7 repeated-measurement sets per infant on average. Interclass correlation between muscle thickness and muscle strength was $r = 0.61$ ($P < .001$), between muscle thickness and motor development was $r = 0.81$ ($P < .001$), and between muscle strength and motor development was $r = 0.76$ ($P < .001$).

**DISCUSSION**

This study showed that muscle thickness was significantly decreased in the biceps brachii, forearm flexors, quadriceps, and tibialis anterior muscle compared with normal muscle structure (as measured by muscle echo intensity). We showed for the first time that in infants with PWS, decreased muscle thickness in specific muscle groups is strongly associated with decreased muscle strength and motor performance. GH treatment combined with physical training significantly increased muscle thickness, which was matched by an increase in muscle strength and motor development.

Our finding of decreased muscle thickness in infants with PWS is in line with the reported lower LBM in infants with PWS and the early findings of type 2 muscle fiber atrophy and smaller type 1 muscle fiber size in infants with PWS. Some studies reported that GH increases LBM (mainly determined by muscle mass), but, however, in these studies, the interpretation of the reported results is problematic because the increase in LBM was not corrected for changes in height. Studies in children with PWS that reported height-corrected LBM have found that LBM normally decreases over time, but with GH treatment LBM stabilizes. In contrast to treatment in later childhood, GH treatment in infancy leads to an improvement in height-corrected LBM. Our study results confirm these findings.

Another interesting finding is that muscle thickness at baseline varied widely between infants, which is in accordance with clinical observations that hypotonia and muscle strength also show considerable variation. This finding might be related to innate or prenatal predispositions. Future studies in larger groups should focus on the relationship between muscle thickness and motor development in relation to chromosome 15q11-q13 deletion, uniparental disomy, an imprinting center defect, or balanced translocations.

In this study, changes over time also revealed differences between the biceps brachii and tibialis anterior and the forearm flexors and quadriceps. In the former muscle groups, muscle growth rate was in line with muscle growth in developmentally normal infants, although at a lower level during the physiotherapy-only period. The GH treatment led to an

### TABLE 3 Results of the 4 Multilevel Regression Models for Muscle Thickness Development

<table>
<thead>
<tr>
<th>Biceps</th>
<th>Forearm</th>
<th>Quadriceps</th>
<th>Tibialis Anterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachii</td>
<td>Flexors</td>
<td>Anterior</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−3.983</td>
<td>−7.522</td>
<td>−6.673</td>
</tr>
<tr>
<td>Age</td>
<td>−0.005</td>
<td>0.183**</td>
<td>0.162**</td>
</tr>
<tr>
<td>GH</td>
<td>0.902**</td>
<td>0.906**</td>
<td>0.794 **</td>
</tr>
<tr>
<td>Baseline average muscle thickness</td>
<td>3.442**</td>
<td>5.847 **</td>
<td>3.420**</td>
</tr>
<tr>
<td>Age × baseline average muscle thickness</td>
<td>—</td>
<td>−0.145**</td>
<td>−0.102**</td>
</tr>
<tr>
<td>Between-subject variance intercept</td>
<td>0.018</td>
<td>0.002</td>
<td>0.200</td>
</tr>
<tr>
<td>Between-subject variance age</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Within-subject variance</td>
<td>0.67</td>
<td>0.28</td>
<td>0.65</td>
</tr>
<tr>
<td>Variance empty model</td>
<td>1.14</td>
<td>0.95</td>
<td>1.28</td>
</tr>
<tr>
<td>Proportional reduction in unexplained variance, %</td>
<td>41</td>
<td>71</td>
<td>49</td>
</tr>
</tbody>
</table>

Results include the explanatory variables (age, GH, and baseline muscle thickness) and their interactions. Explanatory variables: age = age in months; GH = a Boolean variable (0 = no, 1 = yes); baseline average muscle thickness = sum of muscle thickness per muscle group divided by 4. *$P < .01$, **$P < .001$.

* The reduction in the unexplained variance when the empty model is compared with the final model.
increase in the rate of growth in muscle thickness, which leveled out subsequently. In these muscle groups, infants with smaller muscles at baseline continued to have relatively smaller muscles throughout the study. In the forearm flexors and quadriceps, however, catch-up growth was observed even during the physiotherapy period; this catch-up growth manifested as an increase in growth rate compared with muscle growth in developmentally normal infants and infants with PWS. Acquisition of the first fundamental skills during early motor development relies more on use of the forearm flexors and quadriceps than the biceps brachii and tibialis anterior. After the typically severe hypotonic phase, infants with PWS demonstrate more spontaneous movements. However, the order differs from typical infant development: head control, for instance, is easier in a vertical position than in a horizontal lying position, and the infants start to reach and grasp while using a supporting surface to overcome the influence of gravity. The forearm flexors are used more than the biceps brachii for the manipulation of objects, because infants use pronation of the forearm frequently but do not yet lift objects. The quadriceps and foot extensors are used when infants learn to push themselves forward across the floor and to stand and walk. In the early phase of walking, infants do not use dorsal flexion of the feet, so they do not train the tibialis anterior as much as the quadriceps. This pattern of motor development may explain the differences in muscle growth between the 4 muscles in infants with PWS and suggests that
a training effect is strengthened by GH treatment.

The statistical procedure we used showed that, over time, changes in muscle thickness were highly correlated to muscle strength and motor performance in each individual with PWS. One of the largest differences between muscle strength training in adults and children is that, in children, an increment in muscle strength does not go hand in hand with an increment of muscle thickness, so we hypothesize that GH is responsible for the increment in muscle thickness. However, whereas muscle thickness improved over time to the lower normal range, motor development remained seriously delayed whereas muscle thickness improved over time. Therefore, it was not possible to evaluate the direct effect of GH on muscle strength. However, the strong correlation between changes in muscle thickness and changes in muscle strength and motor performance in infants with PWS supported our hypothesis that GH improves muscle strength and motor development by increasing muscle thickness in PWS infants.

CONCLUSIONS

GH has a positive effect on muscle thickness in infants with PWS. Muscle thickness is highly correlated with muscle strength and motor performance. In muscles that are used a lot in the acquisition of fundamental skills in early motor development, there was a naturally occurring catch-up in growth independent of GH treatment, suggesting a training effect.

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