Association between Foot Growth and Musculoskeletal Loading in Children with Prader-Willi Syndrome before and during Growth Hormone Treatment

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Objective To explore how foot growth relates to musculoskeletal loading in children with Prader-Willi syndrome (PWS).

Study design In 37 children with PWS, foot length (FL) before and after 6 years of growth hormone therapy (GHT) was retrospectively evaluated with parental and sibling's FL, height, and factors reflecting musculoskeletal loading, such as weight for height (WfH), lean body mass (LBM; dual energy X-ray absorptiometry, deuterium labeled water), physical activity (accellerometry), and walk age. Because of the typically biphasic evolution of body mass and the late walk age in PWS, 2 age groups were separated (group 1, >2.5 years; group 2, ≤2.5 years).

Results Children with PWS normalized height, but not FL after 6 years of GHT. Parental FL correlation with PWS's FL was lower than with sibling's FL. In group 1, FL positively correlated with WfH, LBM, and physical activity. In group 2, FL negatively correlated with age at onset of independent ambulation. Foot catch-up growth with GHT was slower in group 2 compared with group 1.

Conclusion In PWS, FL is positively associated with musculoskeletal loading. Small feet in children with PWS before and during long-term GHT may be more than just another dysmorphic feature, but may possibly reflect decreased musculoskeletal loading influencing foot growth and genetic and endocrine factors. *(J Pediatr 2009;154:225-9)*

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by short stature with acromicria (small hands and feet), hypogenitalism with incomplete pubertal development, and cognitive and behavioral problems. Newborns and infants typically have distinct muscle hypotonia and failure to thrive, whereas later in life severe obesity usually is predominant.[1-3] Many symptoms were assumed to be linked to abnormal hypothalamic regulation,[1,4] namely altered energy balance with hyperphagia,[5] hypoactivity,[2] hypogonadism, and growth hormone (GH) deficiency.[6]

In patients with GH deficiency or GH insensitivity syndrome, the size of hands and feet is reduced in proportion to the patient's body height,[7] feet being relatively longer than hands, with both normalizing on GH therapy (GHT).[8] In patients with PWS, however, feet were shown to be relatively smaller than hands,[9] GHT normalizing height and hand length, but not foot length (FL).[10] Normal foot and extremities growth not only depends on GH and genetic factors, but also possibly on musculoskeletal loading, as suggested by these 2 observations: 1) In hemiplegic children, the inactive leg is shorter than the active one;[11] and 2) In patients with meningomyelocele, lower extremities are longer in individuals walking than in those using a wheelchair.[12] It may be neural or muscle dysfunction causing reduced extremities' growth in these conditions; however, the possible association between growth of the extremities and musculoskeletal loading leads us to this hypothesis: In children with PWS, the relative reduction in foot growth may be caused by reduced physical activity, resulting in decreased musculoskeletal loading.

The aim of this study was to explore in children with PWS the relationship between FL and different markers of musculoskeletal loading against the backdrop of parental and

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D_2O	Deuterium labeled water	LBMHt	Lean body mass corrected for sex and height
DEXA	Dual energy X-ray absorptiometry	PWS	Prader-Willi syndrome
FL	Foot length	WfH	Weight for height
GHT	Growth hormone therapy		
LBM	Lean body mass		

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siblings' FL and GHT. We analyzed data of 2 different groups of children before and during GHT: 1 group consisted of young underweight children not yet or just having started independent ambulation, and the other group of older overweight children walking for several years.

METHODS

This observational study was part of a prospective long-term open treatment trial,[6] in which data were retrospectively re-analyzed. Thirty-seven pre-pubertal children (age, 4.0 ± 3.9 years; 19 girls, all prepubertal) with genetically proven PWS (paternal deletion, n = 15; maternal unidisomy, n = 22) were divided in 2 groups, those older than 2.5 years (group 1) and those younger than 2.5 years (group 2) at the start of recombinant GHT (Genotropin, Pfizer, Duebendorf, Switzerland). Two to 2.5 years is the age when most children with PWS start independent ambulation[13]; in group 2, therefore, children were young, typically underweight, and not yet walking; in group 1, children were older, typically overweight, and had been walking for several years (Table I; available at www.jpeds.com). GHT was given as a daily subcutaneous injection at a dose of 0.025 mg GH/kg (approximately 6 mg/m^2 per week). All subjects received equal levels of physical and motor developmental therapy. Auxological measures and body composition analysis were performed before and during 72 months of GHT. The study, including measurements of anthropometry, physical activity, body composition, GHT, and the retrospective analysis were approved by the Ethics Committee of the Children's University Hospital of Zurich, and informed consent was obtained from all parents or guardians.

In all patients, height and weight were measured with standard techniques.[14] FL was measured by using the foot-measure rule according to the standards of Oosterwolde.[15] Data are given as standard deviation score (SDS) to scale the data for comparison across ages and sex, referring for children and adults to the first Zurich Longitudinal Study and the Oosterwolde study, respectively.[14,15] Weight for height (WfH) was used to express body mass: because of the reduced initial height of untreated children with PWS and the changes in height and body composition expected with GHT, this is the most adequate representation of body mass.[16]

Parental and siblings' self-assessed height and FL was implemented with detailed oral and written instructions; the parents measured their partner and the siblings. Height was measured standing against a wall with a rectangle; naked FL was measured in a standing position with a foot-measure rule; the mean out of 3 measurements was recorded. Data were expressed in SDS on the basis of a healthy population without PWS.[15] Parental and siblings' SDS were derived as the mean of mothers' and fathers' SDs and of the corresponding siblings' SDS for FL and height, respectively.

Depending on the age group studied, musculoskeletal loading was quantified directly by measuring physical activity[2] or indirectly by assessing lean body mass (LBM) or age at onset of independent ambulation.

Objectively measured physical activity data were available for 13 of the 17 children of group 1 (group 1b, Table I). Physical activity was measured on 3 consecutive days by the mean daily walking distance assessed with accelerometry (Mechanical Pedometer, Eschenbach, Germany). These data have been published previously.[2]

LBM was taken as an indirect measurement for physical activity. In children with PWS, the severely reduced LBM[2,16,17] was shown to be the consequence of low physical activity—if children with PWS were increasing their physical activity, their LBM increased in parallel.[2] LBM was measured in group 1 (Table I) with dual energy X-ray absorptiometry (DEXA, Hologic QDR-2000, Waltham, Massachusetts; software version 7.10B).[16] In the younger children (group 2), LBM was assessed with stable isotope dilution measuring total body water with deuterium labeled water (D_2O); LBM was derived from age-dependent hydration coefficients as described earlier.[18,19] Both methods measure lean LBM with similar accuracy (1%-4% for DEXA and 2%-4% for D_2O).[20] LBM was expressed as SDS corrected for sex and height (LBMHt) with previously published age- and method-specific reference data.[19,21] To compare LBM in the groups equal SDS levels for LBM_{D2O} and LBM_{DEXA} were assumed on the basis of studies in young healthy adults.[22] Because body composition measurements were not available for every child, body compositional analysis refers to subgroups (Table I), group 1a (children >2.5 years measured with DEXA) and group 2a (children ≤2.5 years measured with D_2O).

The age at which children started independent ambulation as reported by parents of children with PWS was taken as an indirect measurement for musculoskeletal loading of the feet.

All data are given as means and SDs. Differences among parents, patients, and their siblings and changes induced with GHT after 72 months were tested with the paired Student t test. Differences in the groups were tested with t test for independent variables. For linear correlation analysis, the Pearson test was used. Multiple regression models with hierarchical backward exclusion of the variables were computed by using SPSS software for Windows. P values $< .05$ were considered to be significant.

RESULTS

Of the 37 PWS families, data were not available for 2 mothers and 4 fathers; 10 subjects had no siblings; data for all siblings were available (27 PWS families, 20 sisters, 28 brothers). Mean (SD) parental height and FL were −0.10 (1.05) SDS and −0.29 (0.95) SDS, respectively (Figure 1A and B). Mean (SD) for height and FL of the siblings were 0.08 (1.19) SDS and −0.32 (1.34) SDS, respectively. Height SDS and FL SDS between parents and siblings were not significantly different ($P_{height} = 0.50$ and $P_{foot\ length} = 0.65$).

The mean (SD) age of children with PWS of group 1 and 2 was 7.4 (3.4) years and 1.2 (0.6) years, respectively. Mean (SD) height in patients with PWS was low before GHT (group 1, −1.87 [1.37] SDS; group 2, −2.28 [1.47]

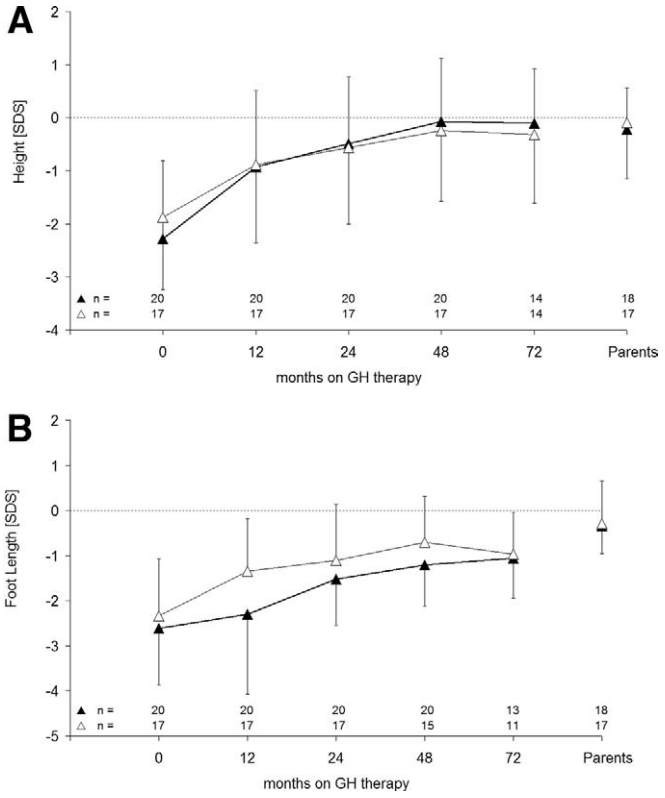

Figure 1. **A,** Height (SDS) and **B,** foot length (SDS) at baseline and for as long as 72 months of GH therapy. △, group 1 (>2.5 years); ▲, group 2 (≤2.5 years). Parental height (SDS) is indicated.

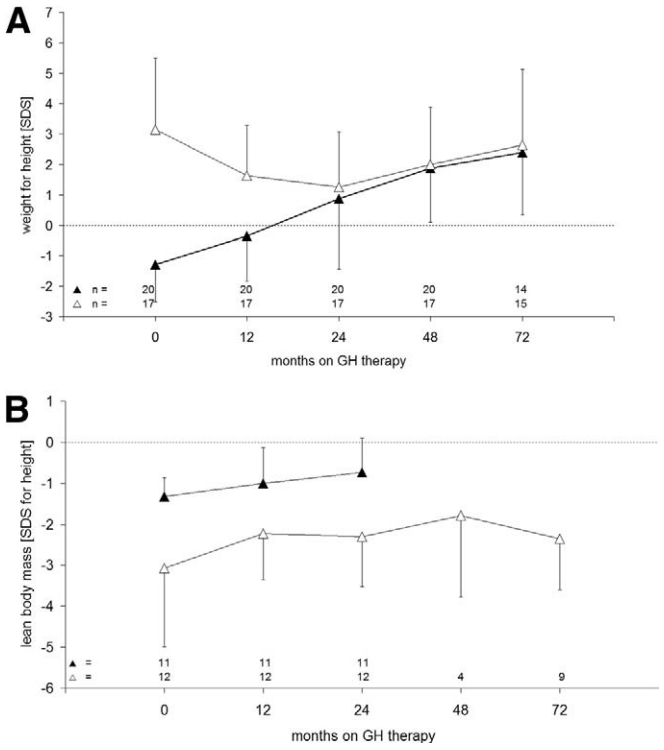

Figure 2. **A,** Weight for height (SDS) and **B,** lean body mass (SDS for height) at baseline and for as long as 72 months of GH therapy. △, group 1 (>2.5 years); ▲, group 2 (≤2.5 years).

SDS; Table I). Mean height SDS significantly increased after 72 months of GHT ($P < .0001$), not differing significantly from parental target height (Figure 1A) and sibling's height SDS ($P > .05$).

Mean FL (SD) was low before GHT (group 1, −2.33 [1.27] SDS; group 2, −2.61 [1.26] SDS); it increased significantly after 72 months of GHT ($P < .0001$). Mean first year catch-up of FL SDS (FL SDS at month 12 − FL SDS at month 0) in group 1 and group 2 were 1.0 (0.5) SDS and 0.3 (1.2) SDS, respectively ($P = .043$). After 72 months of GHT, the DL SDS for both groups remained significantly lower than the mean parental FL SDS ($P < .001$; Figure 1B).

Mean WfH (SD) in group 1 was high before treatment (3.15 [2.35] SDS; Table I); it transiently decreased during the first 2 years of GHT ($P < .001$), and increased again thereafter. At 72 months of GHT, there was no longer a difference compared with baseline ($P > .05$). In group 2, mean WfH was low at baseline (−1.28 [1.23] SDS; Table I), and increased continuously during 72 months of GHT ($P < .0001$; Figure 2A).

Mean LBMHt in both groups was low at baseline (group 1, −3.07 [1.91] SDS; group 2, −1.32 [0.46] SDS) and at all times with GHT. There was a significant increase during the first 24 months of GHT (group 1, $P = .05$ and group 2, $P < .02$ compared with baseline); thereafter LBMHt (measurements being available in 9 children only, group 1a) stayed unchanged (Figure 2B).

The mean age when children of group 1 and 2 started independent ambulation was 2.23 (0.79) years and 1.93 (0.29) years, respectively. The difference was not significant ($P = .14$). In group 1, mean physical activity, assessed with daily walking distance, was 11.45 (7.53) km/day.

Height and FL SDS between parents and siblings were highly correlated ($r_{height} = 0.87$, $r_{foot\ length} = 0.75$, $P < .001$). Height SDS and FL SDS of parents and their children with PWS were positively correlated at baseline ($r_{height} = 0.37$, $r_{foot\ length} = 0.41$, $P \leq .03$). This baseline correlation was similar including pairs with completed 72-month data only. Before starting GHT in children with PWS, FL SDS was positively correlated with height SDS (Table II). In group 1, FL SDS was positively correlated with WfH SDS and LMHt SDS. In group 2, FL SDS was negatively correlated with the age when children started independent ambulation (Table II).

After 72 months of GHT, there was no correlation between height SDS or FL SDS of parents and their children with PWS, respectively ($r_{height} = 0.24$, $r_{foot\ length} = 0.24$, $P > .11$). In children with PWS, after 72 months of GHT, FL SDS was positively correlated with height SDS, but not with WfH SDS. In group 1, FL SDS was positively correlated with LMHt SDS; the correlation between FL SDS and physical activity measured after 48 months on GHT approached statistical significance ($P = .09$). In group 2, after 48 months on GHT, FL SDS was negatively correlated with the age when children started independent ambulation (Table II).

Multiple regression models of baseline data were com-

Table II. Correlations between foot length SDS and various endpoints of children with Prader Willi syndrome before and after 72 months on growth hormone therapy

	Total group		Group 1		Group 2	
	Before GHT	During GHT	Before GHT	During GHT	Before GHT	During GHT
Height (SDS)						
r	0.77	0.78	0.81	0.82	0.75	0.78
P	.00	.00	.00	.00	.00	.00
WfH (SDS)						
r	0.33	0.02	0.51	0.39	0.33	−0.2
P	.02	NS	.02	NS	.08	NS
LBMHt (SDS)						
r	0.28	—	0.58	0.83	0.36	—
P	NS	—	.03	.02	NS	—
Physical activity (km)*						
r	—	—	—	0.42	—	—
P	—	—	—	.09	—	—
Walk age (years)						
r	−0.40	−0.46	−0.06	−0.02	−0.55	−0.65
P	.01	.02	NS	NS	.01	.01

NS, Not significant.
*After 48 months on GHT, not significant for $P \geq .1$.

puted to investigate the relative importance of measures of musculoskeletal loading of the feet on FL compared with effects of height and parental FL. In the total group, the final model including height SDS, walk age, and LBMHt SDS explained 71% of the total variance of FL SDS ($P < .001$; Table III, available at www.jpeds.com). WfH SDS and parental FL SDS dropped out. In group 1, the final model including height SDS and LBMHt SDS explained 78% of the total variance of FL SDS ($P = .001$; Table III). WfH SDS, parental FL SDS, and walk age dropped out. In group 2, the final model including height SDS, parental FL SDS, and walk age explained 79% of the total variance of FL SDS ($P = .019$; Table III); WfH SDS and LBMHt SDS dropped out.

DISCUSSION

Factors other than GH and the genetic background may have an impact on foot growth. At least for children with PWS, this is suggested by these 2 lines of evidence: In children with PWS, we found a significantly delayed and incomplete foot catch-up growth after 3[10] and 6 years of GHT, whereas height and hand length normalized after 2 years of GHT.[10] As opposed to PWS in children born small for gestational age or with GH deficiency, FL and height and hand length fully normalized after 3 years of GHT.[8,23] Because of the common genetic background of the family, FL of parents and their children is expected to be highly correlated. We confirmed this positive correlation for parents and their healthy children (siblings of children with PWS); however, for parents and their children with PWS, the correlation of FL was smaller before and even absent after 72 months of GHT.

Musculoskeletal loading was quantified by surrogate variables such as age at onset of independent ambulation, body mass expressed with WfH, and physical activity measured with pedometers or LBM. LBM was shown earlier to be a strong predictor of physical activity in children with PWS.[2,17]

Our study supports the positive impact of musculoskeletal loading on foot growth with 5 lines of evidence. First, in the younger group of PWS children, there was a significant negative correlation between the age at onset of independent ambulation and FL—the later the onset of musculoskeletal loading, the shorter the FL. As expected this association was absent in the older group of children who had been walking for several years. Second, in the older group of children only, there was a significantly positive correlation between FL and WfH, indicating that body mass may be a stimulus for foot growth. Third, first year foot catch-up growth on GHT was significantly delayed in the younger children with PWS compared with the older children with PWS, suggesting that in this group of children, musculoskelatal loading may promote foot catch-up growth. Fourth, in the older children only, we found a positive correlation between FL and LBM. Finally, in this same group, there was a trend toward a positive correlation between FL and physical activity. The multiple regression models also support the effect of musculoskeletal loading expressed with body mass (WfH), height-corrected LBM, and walk age on baseline measures of FL in children with PWS; in addition to height, parental FL variables of musculoskeletal loading were significant predictors of FL measures.

The positive association between musculoskeletal loading and FL suggests that mechanical factors impact foot growth regulation. This concept is comparable to the "muscle-bone unit" used to explain the interdependency between bone strength (bone remodeling) and muscle strength in healthy adults and adolescents.[24]

This analysis is limited by the retrospective study design

and the relatively small number of patients. However, we conclude that persisting small feet in children with PWS on long term GHT may be more than just another dysmorphic feature, but possibly reflect decreased musculoskeletal loading demonstrating a new element of foot growth regulation.

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Table I. Baseline data before growth hormone therapy was started, separated in 2 groups according to age at onset of growth hormone therapy

	Group 1 (>2.5 years)			Group 2 (≤2.5 years)	
	Total	Accelerometry (group 1b)	DEXA (group 1a)	Total	D_2O (group 2a)
n (f)	17 (9)	13 (7)	12 (7)	20 (10)	11 (7)
Age (years), Mean ± SD (range)	7.35 ± 3.38 (3.01-14.59)	6.97 ± 2.93 (3.01-13.38)	8.27 ± 3.18 (4.87-14.59)	1.16 ± 0.58 (0.35-2.32)	1.20 ± 0.54 (0.42-1.89)
Height (SDS), Mean ± SD (range)	−1.87 ± 1.37 (−4.82-0.00)	−1.72 ± 1.0 (−4.31-−0.40)	−1.89 ± 1.42 (−4.82-−0.40)	−2.28 ± 1.47 (−5.70-−0.50)	−2.70-1.55 (−5.70-−0.50)
WfH (SDS), Mean ± SD (range)	3.15 ± 2.35 (−2.78-6.38)	3.59 ± 1.95 (−1.24-6.38)	3.77 ± 1.52 (0.84-6.38)	−1.28 ± 1.23 (−3.04-1.97)	−1.14 ± 1.03 (−2.39-0.37)

No significant difference was found between sub-groups and their respective total groups.

Table III. Multiple regression models with hierarchical backward inclusion for the total group, for group 1 and group 2 including parental foot length SDS, walk age, and baseline data of height SDS, weight-for-height SDS and lean body mass corrected for sex and height SDS as independent variables

	Total group			Group 1			Group 2		
Model	**B**	**t**	***P* value**	**B**	**t**	***P* value**	**B**	**t**	***P* value**
First									
Constant	0.33	0.45	.656	2.84	1.09	.317	−0.08	−0.06	.953
Height SDS	0.52	4.70	<.001	0.59	3.44	.014	0.45	2.96	.042
pFL SDS	0.23	1.26	.227	0.03	0.13	.902	0.68	1.66	.172
Walk age (years)	−0.57	−1.93	.071	−1.52	−1.22	.270	−0.70	−2.16	.097
WfH SDS	0.05	0.69	.501	−0.01	−0.05	.964	−0.20	−0.50	.647
LBMHt SDS	0.25	2.35	.032	0.37	2.76	.033	0.04	0.04	.971
Final									
Constant	0.55	0.81	.431	−0.11	−0.26	.804	−0.11	−0.16	.877
Height SDS	0.57	5.54	<.001	0.63	4.28	.002	0.42	3.33	.016
pFL SDS							0.68	2.04	.087
Walk age (years)	−0.63	−2.21	.041				−0.63	−2.46	.049
WfH SDS									
LBMHt SDS	0.24	2.46	.024	0.32	2.93	.017			

pFL, Parental foot length.