

Body Composition Abnormalities in Children with Prader-Willi Syndrome and Long-Term Effects of Growth Hormone Therapy

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Key Words

Prader-Willi syndrome · Prader-Labhart-Willi syndrome · Body composition · Fat mass · Lean mass · Growth hormone therapy · Syndromal obesity

changes the phenotype of children with PWS: fat mass becomes normal, but, at least in the setting studied, GH is not sufficient to normalize lean tissue mass.

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Abstract

Obesity and hypothalamic GH deficiency contribute in different ways to the disturbances of body composition in Prader-Willi syndrome (PWS); while both increase the fat compartment, the reduction of lean tissue mass has been attributed mainly to GH deficiency. Therefore, body composition measured by dual-energy X-ray absorptiometry was prospectively studied in 12 overweight children with PWS and weight for height (WfH) SDS >0 before and during 3.5 years of treatment with hGH (0.037 mg/kg/day) on average. In the long term, there is a net reduction of body fat from 3.1 to 1.2 SD, with a minimum at the end of the second year of treatment. WfH SDS correctly reflects body fat mass and its changes. The initial deficit of lean mass (–1.6 SD) is counteracted by GH only during the first year of therapy (increase to –1.25 SD). But in the long term, GH therapy does not further compensate for this deficit, when lean mass is corrected for its growth-related increase. In conclusion, exogenous GH

Introduction

Obesity is the growing epidemic of industrialized countries and there is no simple remedy, because it is the result of a variety of underlying pathogenetic factors. Therefore, rare monocausal syndromal forms of obesity, such as Prader-Willi syndrome (PWS), are increasingly attractive models to evaluate specific pathogenesis. With an estimated incidence of 1:15,000, PWS remains the most frequent form of genetic obesity. Its main features, namely polyphagia, obesity, short stature, hypogonadism, muscle hypotonia and mental retardation, are linked to a hypothalamic dysfunction, which has not yet been comprehensively described. Nevertheless, evidence increases that, even though difficult to diagnose, there is a hypothalamic GH deficiency accounting not only for short stature and increased fat mass, but also for the decreased absolute lean body mass [1] – in contrast to nonsyndromal obesity.

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Table 1. Clinical data of children with PWS

Patient No. (n = 12)	Sex (7 f, 5 m)	Age ^a years	Pubertal stage ^{a, b} B or G	Height ^a SDS	Weight for height ^a , SDS	Study period months
11	F	3.70	1	-1.90	4.14	42
12	M	6.70	1	-0.60	3.00	24
13	F	5.00	1	-0.80	3.16	42
14	F	6.80	1	-2.08	6.38	42
15	M	6.80	1	-1.40	4.37	42
16	M	7.00	1	-1.60	4.34	42
17	F	7.10	1	-2.43	0.84	42
18	M	9.50	1	-2.10	3.76	42
19	F	11.10	2	-0.40	5.31	12
21 ¹	F	13.30	2-3	-4.31	4.31	12
22 ²	M	13.50	3	-0.74	12.04	36
23 ³	F	14.60	2-3	-4.82	1.57	42
Median		7.1	1	-1.75	4.23	42
Range		3.7 to 14.6	1 to 3	-4.82 to -0.4	0.84 to 12.04	12 to 42

Substitution: ¹ With ethinylestradiol since age 14.5 years; ² with testosterone 100 mg i.m. since age 14.8 years; ³ combination of estradiol/progesterone since age 16.6 years.

^a Values at the beginning of therapy.

^b Pubertal stage according to Tanner; B = breast stage in female and G = genital stage in male patients.

The reduced lean mass might contribute to muscle hypotonia and decreased motor activity, thereby further compounding obesity. Since the disturbance of body composition and its sequels are the main causes of morbidity and mortality [2, 3], therapy should first aim at reducing fat mass and, second, at increasing muscle mass. It has been shown that these patients may benefit from the fat-reducing and anabolic properties of GH [4–8], but the longer-term outcome of GH therapy is uncertain. We focussed on whether fat mass is reduced in the long term. We further wanted to quantify the initial muscle mass deficit and its potential compensation during GH therapy.

The aim of the study was not to achieve normal height in PWS, but height course was monitored to test sustenance of growth-anabolic GH effects; weight for height (WfH) was evaluated to verify whether it is an easily assessable clinical parameter correctly reflecting body fat mass.

Patients and Methods

Twelve children with PWS, documented by deletion or uniparental disomy of chromosome 15, were studied prospectively (table 1). The long-term effects of GH on growth [9] and the 1-year results of physical performance and well-being have been published earlier [6].

All children with PWS and overweight, defined as WfH standard deviation score (SDS) > 0, were included (table 1), 8 being prepubertal and 4 pubertal (Tanner breast or genital stages 2 and 3). The children not included with WfH < 0 were all younger than 4 years. Missing values were not due to dropouts, but to uncompleted investigation intervals as a result of delayed start of therapy (missing at 42 months).

The children were treated with 24 IU/m²/week (~ 0.037 mg/kg/day) recombinant hGH (Pharmacia & Upjohn, Dübendorf, Switzerland), administered in daily subcutaneous injections for 3.5 years on average. The study has been approved by the Ethics Committee of the Children's University Hospital of Zürich and informed consent was obtained by the parents. No additional medication was administered besides sex steroids in 3 pubertal patients with hypogonadism after the age of 14.5 years and after 18 months of GH therapy. The patients were advised to continue their diets, adapted to the recommendations of the Prader-Willi Syndrome Association of USA [10]. Food intake was monitored by records; in general, the energy intake (median 11.3, range 8–13.4 kcal/cm height) was 20–40% less than recommended for healthy children.

Height and WfH were assessed 6-monthly by the first author according to standard techniques [11] and are given as SDS (individual value – reference mean divided by SD) to scale the data for comparison across ages and sex, using the First Zürich Longitudinal Study [11]. WfH was used instead of weight for age: In consideration of the reduced initial height of untreated children with PWS and the changes to be expected during GH therapy, this is the most adequate representation of body mass.

Body composition was determined before therapy, and then after 6, 12, 24, 36 and 42 months in all children by dual-energy X-ray absorptiometry (DEXA) (Hologic QDR-2000, Waltham, Mass.,

Fig. 1. Height SDS in children with PWS (prepubertal □, n = 8 and pubertal ◆, n = 4) before and under up to 3.5 years of GH therapy, as medians (solid lines) as well as minimum and maximum of the combined group (broken lines). Significant differences in the combined group of prepubertal and pubertal children versus the value before therapy are indicated as * p < 0.05, ** p < 0.01.

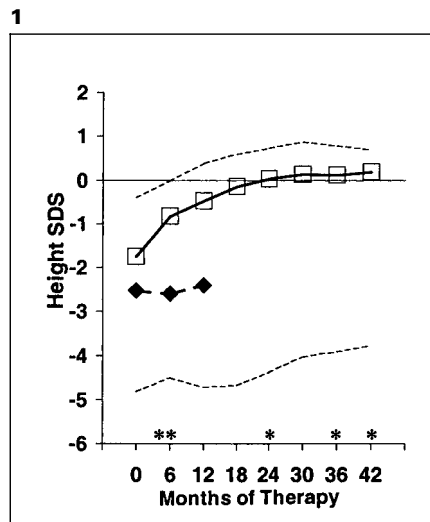
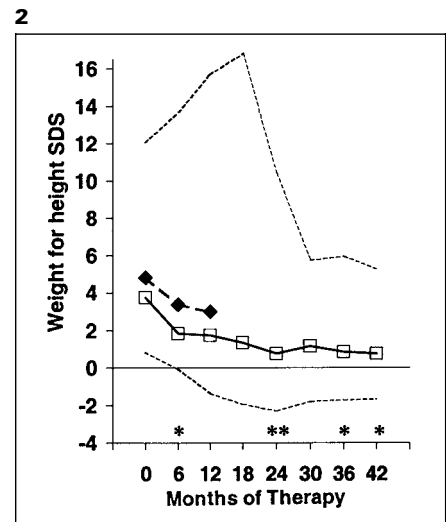


Fig. 2. Weight for height SDS in children with PWS, before and under up to 3.5 years of GH therapy (symbols as in figure 1).



USA; software version 7.10B). Lean tissue mass (LTM) was calculated as fat-free mass minus bone mineral content. Lean and fat mass were compared to two sets of reference data:

(1) Reference values measured with the same DEXA method, but in a different population (in part published previously [12, 13]): Data are given as SDSs based on prediction models established in female (n = 412) and male (n = 479) Caucasian US American children covering the age range of 0.3–19 years, scanned in a Hologic QDR-2000 (pencil-beam mode, body composition software version 5.56). Various combinations of age and height, using fractional and integer powers and log transformations, were tested for development of the prediction model. The following model provided the best overall prediction (lowest SEE) of LTM for the reference population:

$$\ln(\text{LTM}) = a \ln \text{Ht} + b \text{Age} + c$$

with gender-dependent constants:

$$a = 1.836 \text{ or } 1.995, b = 0.0327 \text{ or } 0.0136, \\ c = 6.0811 \text{ or } -6.7647 \text{ for males or females, respectively.}$$

Using this model, the predicted values were calculated for each gender, then grouped into 1-year age intervals, and the SD per age group calculated. Since SD was not independent of age, we successfully established the following linear model:

$$\text{SD}(\text{Age}) = d \text{Age} + e, \text{ where } d = 0.2163 \text{ or } 0.1362, \\ e = 0.323 \text{ or } 0.831, \text{ for males or females, respectively.}$$

For each PWS subject, a predicted LTM was calculated based on their age, gender, and height. The individual SD score was calculated as:

$$\text{SDS for LTM} = (\text{measured LTM} - \text{predicted LTM}) / \text{SD}(\text{Age}).$$

SD scores for fat mass (FM) were calculated similarly:

$$\text{SDS for FM} = (\text{observed fat} - \text{predicted fat}) / \text{SD},$$

whereby predicted fat was derived as a function of age only, since height had little influence.

(2) Reference values measured with a different DEXA instrument (Lunar DPXL), but in a similar European population: Lean tissue and fat mass are calculated as SDS for sex and chronological

age (or height), using a cross-sectional study in Dutch children >4 years of age and with height >100 cm as reference [14]. Therefore, a relation to the healthy reference population was possible in only 7 children of the 8 prepubertal children at the beginning of therapy. We decided to compare our data with the Dutch population, even though small systematic differences in the body composition measurements are known among the DEXA instruments. However, the linear regression between the results for the two DEXA methods is high ($r^2 > 0.95$) and not dependent on BMI [15, 16], hence these systematic differences will not substantially alter the assessment of our longitudinal data.

The relation of LTM exclusively to age could result in a false underestimation, because children with PWS are short for age before GH therapy [6]. Furthermore, we were interested to know whether GH has an additional effect on LTM beyond its growth-related increase. For these reasons, LTM was related to each reference group not only correcting for age and sex, but also for height.

Statistical Methods

As weight and fat-related parameters showed a skew distribution, all values are depicted as medians and ranges. The changes induced by GH therapy after 6, 24, 36 and 42 months were tested by the nonparametric Wilcoxon signed ranks test for paired samples, and p values < 0.05 were considered significant. Linear correlations were tested by Spearman's rank test. All data were processed by GAS 3.3 of the Institute for Medical Informatics (IMI, Zürich, Switzerland).

Results

Anthropometry

Before GH therapy was started, height was below the normal mean in all patients. During the first 36 months of GH therapy it continuously rose to the normal average in prepubertal children (fig. 1), but less consistent changes of height were observed in pubertal patients. WfH decreased

Table 2. Body composition measured by DEXA in 12 overweight children with PWS before and during 3.5 years of GH therapy, compared to two sets of reference data (see Methods)

Overweight PWS children	Before therapy			12 months' GH therapy				42 months' GH therapy			
	mean	range	n	mean	range	n	p*	mean	range	n	p*
% fat	43.7	30.6 to 60.5	12	29.6	23.2 to 57.4	12	0.002	34.3	25.8 to 47.4	8	0.022
Fat SDS-US	2.2	-0.74 to 4.87	12	0.13	-2.43 to 6.23	12	0.010	-0.02	-1.04 to 0.66	8	0.063
Fat SDS-Netherlands	3.14	0.02 to 7.39	11	0.95	0.44 to 9.34	11	0.018	1.23	0.08 to 1.78	7	0.116
Lean SDS-US	-1.61	-2.81 to 0.17	12	-1.25	-2.51 to 2.10	12	0.021	-1.61	-3.26 to 0.77	8	0.735
Lean SDS-Netherlands	-2.95	-5.35 to 1.50	11	-1.79	-4.69 to 0.17	11	0.005	-1.33	-3.50 to -0.66	7	0.028

Data are given as standard deviation scores adjusted for age and sex (SDS-Netherlands), or basing on prediction models (SDS-US); SDS-US for lean mass is additionally corrected for height.

* Level of significance versus values before therapy.

until 24 months of therapy, and then stabilized, the decrease being greatest during the first 6 months (fig. 2) and in prepubertal children, namely 0.76 SD, range -1.7 to 3.0 after 42 months. Detailed data are provided elsewhere [9].

Body Composition

In all patients classified as 'overweight' based on WfH SDS > 0, the percentage of body fat was in fact distinctively elevated (table 2) above the normal range for age-matched children [14], and even for adults (12–28% in males, 15–30% in females). During 42 months of GH therapy, the percentage of fat significantly decreased, as did WfH, but remained slightly elevated. This result, however, in part is conditioned by the deficit of LBM (see below).

Since in PWS, both the compartments of fat mass and of LBM have been described to be adversely affected, they have to be assessed separately and not only in relation to total body mass. For that reason, results are indicated as longitudinal individual courses (fig. 3) of fat SD scores adjusted for age and sex; the correction for height did not change the average results of fat mass and is therefore not shown. Fat mass SDS dropped during GH therapy (table 2, fig. 3), more so during the first 6–12 months (table 2), and was stabilized around the normal mean thereafter. In prepubertal patients, fat mass remained significantly below the initial fat mass until 42 months (table 2). The higher the initial weight, the more fat mass was lost during GH therapy (fig. 3). In some patients, fat mass slightly increased again after 2 years of treatment (fig. 3), but remained in the normal range. Yet the elevation of fat SDS in the overweight patients before therapy was less clear than suggested by the percentage of fat; we assumed

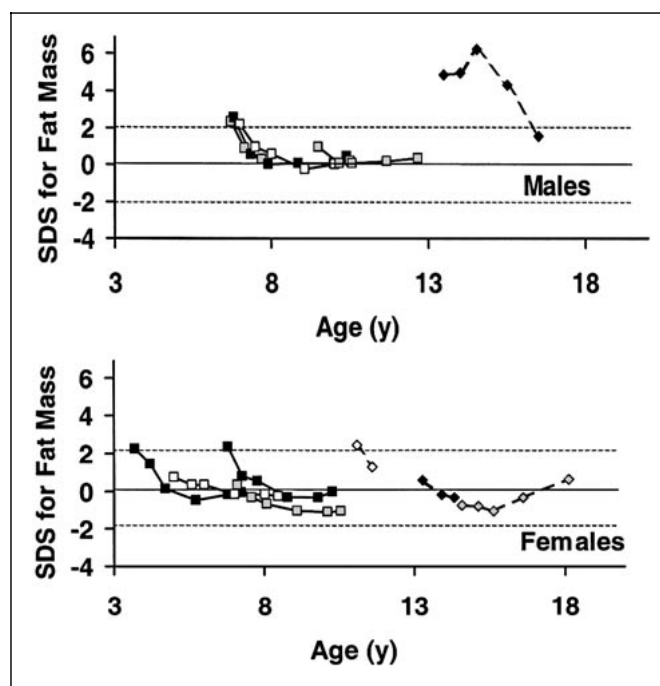


Fig. 3. Total fat mass measured by DEXA in 12 children with PWS, as SD scores corrected for age and sex based on a prediction model, compared to US American children (see Methods); individual courses before and under therapy with GH in young underweight (group 1, triangles), prepubertal overweight (group 2, squares), and pubertal PWS children (group 3, diamonds, dotted lines). Top: boys, bottom: girls.

that this reflects the increasing adiposity of the US American reference population which impedes the delineation of obesity in PWS. Consequently, we also compared the PWS values to Western European references [14]. These data reveal (table 2) that fat mass is clearly increased in

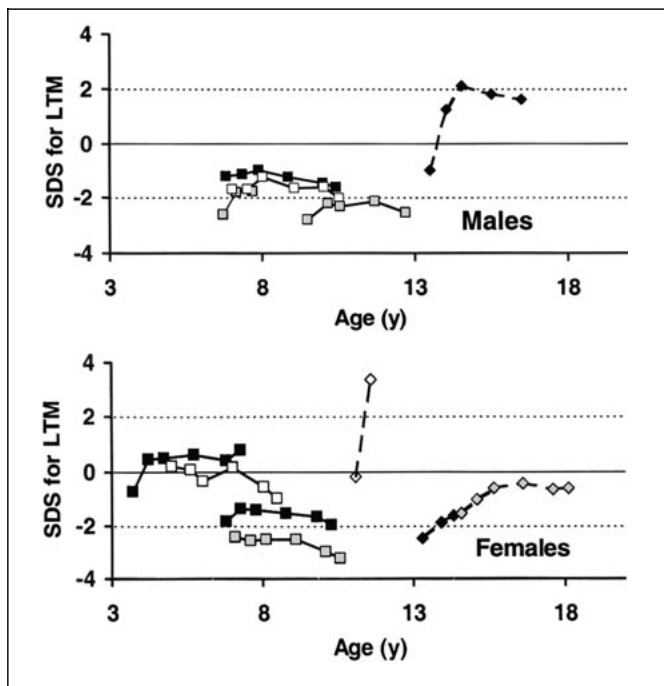


Fig. 4. Lean tissue mass in 12 children with PWS measured by DEXA as SD scores based on a prediction model corrected for height, age and sex, compared to US American children. Top: boys, bottom: girls (symbols as indicated in figure 3).

PWS children when compared to age-matched healthy Dutch children of the same sex. In addition, the pattern of fat loss and the decrease of fat mass by about 2 SD during GH therapy are identical to the changes described by relating the data to US references.

LTM adjusted for height and age (fig. 4) before therapy was reduced to the lower limit of US references in prepubertal PWS children >5 years (fig. 4), but less reduced in the pubertal patients. However, there was no significant increase of lean mass beyond the first 6 months of therapy (fig. 4, table 2). When compared to the Dutch references, the deficit of lean mass was more evident, and also greater in the prepubertal overweight than in the pubertal patients. The results before therapy were substantially the same, irrespective of adjusting for age or height. During GH treatment, a significant increase of LTM was observed in prepubertal and pubertal children, when adjusting for age, though remaining subnormal, with a maximum gain of LTM reached after 6–12 months (table 2). However, when LTM was adjusted for height (data not shown), there was no longer any significant increase of lean mass beyond the first 6 months, similar to the results obtained with the US reference data. This discrepancy

shows that the increase of lean mass reflects the growth-related increase of lean mass, but not a catch-up of the initial deficit of lean tissue – e.g. muscle mass.

The groups were too small to reveal any sex difference of body composition before or during GH therapy in PWS.

Discussion

We report on 12 children with PWS treated with GH during 3.5 years on average. Height in the prepubertal overweight children markedly improved, illustrating that in PWS, the sensitivity to the anabolic effects of GH on growth is not impaired. All overweight children showed a marked and continuous decrease of WfH and, provided treatment had been started before onset of puberty, no longer presented either the obese phenotype or short stature. Thus two major PWS features were no longer present after 3 years of GH treatment in this age group. Until now, a significant weight loss has been shown only in studies up to 24 months of GH therapy [17, 18].

The present study aimed at separately analyzing absolute fat and lean mass in relation to normative data and was thereby faced with several difficulties: First, body composition in children <6 years is measured in only very few studies. We therefore were obliged to accept either a reference group examined by the same DEXA system, but in a US American population with a 2- to 3-fold higher incidence of obesity [19–21], or with an appropriate population (The Netherlands) measured with a different DEXA instrument [14]. Secondly, the reduced height before GH therapy and the catch-up growth during treatment required to adjust the data not only for age and sex, but also for height.

As argued above, the increased fat mass in PWS children is less evident in comparison to the American reference data than in relation to the Dutch data. Nevertheless, the DEXA examination confirms a net reduction of body fat during GH therapy in the prepubertal and pubertal overweight children, with a minimum of body fat mass reached at the end of the second year of treatment. The significant decrease of fat mass after 1 year of therapy has also been shown in several controlled [4, 5] and uncontrolled studies [7, 8]. In one controlled study [22], however, weight, BMI and skin folds were not significantly reduced after 1 year of GH therapy, probably because dietary intake was not considered. Studies in obese adults have shown that GH has a clear fat-reducing effect only if dietary intake is modestly reduced or kept constant, and if

doses from 0.01 to a maximum of 0.05 mg GH/kg/day are administered [23–26].

In the present paper, as well as in two recently published studies [27, 28], the lipolytic GH effect seems to diminish in the long term. As extrapolated from studies in children with GH deficiency, intrauterine growth retardation or Turner's syndrome and in healthy obese adults, the net effects of GH on body composition, induced by lipolysis and protein anabolism, are limited to several weeks [29] or months [30, 31]. It is therefore nevertheless remarkable that GH induces sustained metabolic effects in obese children with PWS. While the metabolic effects of GH are reported to be independent of prior GH secretion [31], it nevertheless has to be pointed out that the dose dependency of the effects of GH on muscular and fat tissue has not yet been investigated in children. The doses used in the PWS studies in general are between 0.03 and 0.04 mg/kg/day, that is 1.5-fold of that administered for substitution in GH deficiency [32]. We also speculate that the fat rebound results from an increased food intake: the monitoring of the diet might be less restrictive due to the parents' emotional relief in view of the weight normalization during GH therapy. This might not be correctly reflected by dietary protocols, which showed an energy intake reduced by at least 20% compared to healthy children. Further studies on the balance of energy metabolism in PWS and parental educational behavior are being conducted.

PWS patients can store fat with a smaller gain of fat-free mass [33] compared to healthy obese children; the reduction of lean mass in spite of obesity [1] has been attributed to the hypothalamic GH deficiency in PWS [34]. In fact, in the present study, a marked decrease of lean mass was documented before therapy, in comparison to the Dutch reference children, but this deficit of LTM was smaller in comparison to American children. In the pubertal patients, the less reduced lean mass before therapy and the subsequent increase might be overlapped by the additional effect of endogenous and exogenous androgens.

Several studies [4, 5, 7], including our own [6], have demonstrated that lean mass increases after 1 year of GH therapy. Provided the data are related to age only, this remains so even after 3.5 years. This study is the first to show, however, that no long-term additional gain of muscle mass beyond the first year was achieved by GH therapy, when lean mass is corrected for its growth-related increase. In contrast to what could be concluded from basal studies [34] or 1-year GH treatments [4–7], GH therapy not even in the long term compensated for the initial deficit of lean mass. This matches the observations in children with and without GH deficiency under GH therapy

[30, 31], where muscle catch-up growth was maintained only during the first 6–12 months and then returned to a steady state. We conclude that GH alone – at least in the dosage administered – is not sufficient to normalize lean body mass; even under 10 years of GH substitution in GH-deficient adults, a substantial lack of lean mass compared to healthy controls has been reported recently [35]. It is evident that any growth of muscles, the main constituent of LTM, depends on physical training and not on hormones alone. Therefore, the initial approach to improve muscle mass in PWS by GH therapy solely was somewhat mistaken, even though a – still insufficient – increase of physical activity has been described [4, 6]. This might be the main clue in PWS: physical inactivity and muscle hypotonia, probably induced by a defective CNS regulation, result in decreased muscle mass and reduced energy turnover, and finally lead to obesity, which is enhanced by additional hypothalamic defects of appetite regulation and GH secretion. We therefore suggest that a comprehensive care for PWS children has to combine GH substitution with a reduction of energy intake and physical exercise to provide for an efficacious treatment of the somatic deficits of this syndrome. The mental retardation and the compulsive behavior disorder, however, will remain major handicaps.

In conclusion, exogenous GH changes the phenotype of PWS in childhood: height and weight become normal and there is a sustained impact on the net loss of body fat, which nevertheless remains slightly elevated. The long-term effects of exogenous GH on muscle anabolism in PWS are less marked than extrapolated from the observations under the first year of therapy and do not exceed the height-related growth. After 2 years of therapy, there seems to be a loss of sensitivity to the metabolic, but not to the growth-promoting GH effects. In addition to the medical benefit, the disappearance of the obese phenotype of prepubertally GH-treated PWS children relieves the patients and their families of stigmatization.

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