Published in final edited form as:

J Pediatr Adolesc Gynecol. 2018 June ; 31(3): 238–241. doi:10.1016/j.jpag.2017.12.005.

Pubertal Progression in Female Adolescents with Progeria

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Abstract

Study Objective: This study identified the prevalence of menarche and coincident sexual characteristics in female adolescents with Hutchinson-Gilford Progeria Syndrome (HGPS).

Design: Data were examined to determine the prevalence of menarche in female adolescents older than 12 years; all were participants in clinical trials between 2007 and 2016.

Setting: Pediatric hospital in Boston, Massachusetts.

Participants: Fifteen female adolescents, median age 15 (range, 12.0–20.3) years with a confirmed diagnosis of HGPS.

Interventions and Main Outcome Measures: Report of menarche, anthropometric and serum hormonal measures, Tanner pubertal staging, and body composition using dual-energy x-ray absorptiometry.

Results: Nine of 15 (60%) participants reported spontaneous menarche at a median age of 14.4 years (range, 12.0–16.5 years). In those experiencing menarche vs not, median age was older (16.5 vs 13.6 years; $P = .02$), whereas body mass index did not differ (10.5 vs 10.4; $P = .53$) nor percentage body fat (19.4% vs. 19.3%; $P = .98$) or serum leptin levels (0.40 vs 0.40 ng/mL; $P = .23$). Among those who achieved menarche, 2 of 9 (22%) had Tanner II breast development and 2 of 9 (22%) exhibited Tanner II Pubic hair, all reflecting minimal pubertal development. Only early signs of puberty were similarly seen in the non-menstruating group, including 1 of 6 (17%) with Tanner II breasts and 2 of 6 (33%) with Tanner II pubic hair, and Tanner staging did not differ

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The authors indicate no conflicts of interest.

between those who reported menarche vs those who did not (each $P = 1.0$). None of the participants achieved Tanner IV or V thelarche over the course of the study.

Conclusion: Menarche was achieved in more than half of adolescent girls with HGPS, in the setting of little to no physical signs of pubertal development and minimal body fat.

Keywords

Lamin; Progeria; Atherosclerosis; Menarche; Puberty

Introduction

Little is known about pubertal development in children with Hutchinson-Gilford Progeria Syndrome (HGPS), an extremely rare disease (prevalence of 1 in 20 million individuals)¹ of premature aging, and many die during adolescence because of premature atherosclerosis resulting in heart failure.² Children with HGPS exhibit lifelong failure to thrive beginning in the first year of life, with weight and height typically falling well below the 3% percentile by age 2 years.³ Generalized lipodystrophy ensues, with severely low subcutaneous fat and leptin levels.^{4,5} One previous report documented a girl aged 12 years and a young man aged 17 years at Tanner developmental stage II,⁵ suggesting the lack of or a delay in pubertal development among this patient group. Otherwise, puberty has not been studied in these patients.

Classic HGPS is caused by a point mutation in the lamin A/C (LMNA) gene^{6,7} that results in a disease-causing protein called progerin.⁷ Lamin A is an inner nuclear membrane protein that broadly influences nuclear structure and function.⁸ Lamin A as well as progerin are anchored into the inner nuclear membrane by a farnesyl moiety. This anchoring facilitates normal lamin A function and progerin's cellular damage.^{9,10} Several single-site clinical trials have been conducted for children with HGPS, administering inhibitors of protein farnesylation.^{1,3,5} The overarching aims were to improve disease by inhibiting progerin farnesylation and subsequent intercalation into the nuclear membrane.

Materials and Methods

The protein farnesyltransferase inhibitor, lonafarnib, was administered in the first clinical trial, followed by the additional use of the prenylation inhibitors, pravastatin and zoledronic acid, in a second clinical trial. These trials have included large segments of the world's population of children with HGPS, ranging in age from 2 to 22 years. They have afforded the unique opportunity for detailed natural history studies in this extremely rare disease population. Study assessments occurred at months 6, 12, 18, between 40 and 52 months, and at month 60.¹¹ Beyond 60 months, pravastatin and zoledronic acid were discontinued, and patients continued to receive lonafarnib monotherapy. Phone evaluations occurred every 6 months if the patient was not seen at the study site.

Each study visit included a complete history including pubertal milestones, physical examination including Tanner stage evaluation by the same pediatrician, segmental length, fasting weight and body fat evaluation, and serum leptin and albumin measurements. We

also obtained left-sided radio-graphs and determined bone age according to Gruelich and Pyle standards.¹² Segmental whole-body length was used in place of standing height because joint contractures inherent to HGPS can result in an underestimation of true height. Body mass index and body surface area were calculated from segmental length and fasting weight measurements. Body fat was evaluated using a whole body dual-energy x-ray absorptiometry (DXA) scan (QDR Discovery A, Hologic, Inc, Bedford, MA). Measurements were compared with age- and sex-matched controls using pediatric reference software (derived from the multisite, National Institutes of Health-funded Bone Mineral Density in Childhood Study).¹³ With this instrument, the average in vivo precision for body composition (expressed as percent coefficient of variation) for the DXA technologists was less than 1%. Height age calculations were performed by 1 pediatric endocrinologist (C.M.G.) using the median height obtained from Centers for Disease Control and Prevention growth charts (age at which the individual's height corresponded to the 50th percentile). Segmental whole body lengths were used to calculate height age. To generate adjusted bone mineral density Z-scores, the height age or bone age was entered into the scanner, replacing the chronological age.

Data are summarized using descriptive statistics (medians with quartiles, minimums, and maximums; and frequencies). Because of the small sample size and fact that most variables were not normally distributed, statistical comparisons were conducted using Wilcoxon rank-sum tests for continuous variables and Fisher exact test for categorical variables. A one-sample t test was conducted on the mean age of menarche to evaluate whether the mean is significantly different from 14, the estimated mean age of menarche worldwide. Statistical significance was defined as 2-sided $P < .05$.

Results

Fifteen female adolescents with classic HGPS (*LMNA* c. 1864 C > T, G608 G) older than the age of 12 years were identified from among 76 patients who participated in clinical trials at Boston Children's Hospital. Those who experienced menarche are identified as participants 1–9; those who did not are identified as participants A-F. Participants were recruited between May 5, 2007 and December 2, 2014 (age range, 3.3–17.6 years) and followed until January 2017 (age range, 12.8–20.3 years). Nine of the 15 (60%) participants experienced menarche. These patients originated from 12 different countries: United States, Dominican Republic, England, Portugal, Poland, Libya, Argentina, Pakistan, India, Philippines, South Africa, and Japan. Assessments are detailed in Table 1. Nine of the 15 (60%) experienced menarche. Overall, the median age of menarche was 14.4 years (range, 12.0–16.5); 15.4 years for participants who experienced menarche before clinical trial enrollment ($n = 3$) and 14.2 years for participants who experienced menarche after clinical trial enrollment ($n = 6$). The mean age of menarche (14.6 ± 1.4 years) was not significantly different from the established mean age of menarche in healthy female adolescents without HGPS ($P = .25$).¹⁴ As has been shown in our previous studies,^{15,16} bone age was normal in more than half of the participants (Table 1). Among those who experienced menarche, 7 patients (78%) exhibited Tanner I and 2 patients (22%) Tanner II breasts and pubic hair and pubertal development did not differ significantly from the nonmenarche group ($P = 1.0$).

Of the girls who experienced menarche, 4 of 9 (44%) had on-site study evaluations during the 12–18 months before menarche, at which time they were Tanner stage I. Two of these 4 participants had additional postmenarche on-site evaluations. Participant 7 developed sparse pubic hair only and was Tanner stage II at age 15.1 years, which was 10 months postmenarche, and subsequently developed breast buds at age 16.5 years, as evaluated at her on-site visit 27 months postmenarche. Participant 6 had breast buds at the time of her exam, 24 months after menarche at age 16 years.

No participant reached Tanner stage III development for breast or pubic hair. No data were available regarding the cyclicity of the menstrual bleeding. Most participants disclosed that bleeding had occurred at least twice. Two participants reported heavy bleeding with increased flow (menorrhagia) causing anemia. Both participants were prescribed low-dose oral contraceptive agents, which arrested the menstrual bleeding.

Discussion

In healthy adolescent girls, menarche is typically a late pubertal event, after the gradual development of breasts and pubic hair, the pubertal growth spurt, and changes in body composition that are characterized by increasing body fat. Some previous studies have suggested menarche and regular menstrual function in healthy adolescents and women to be dependent on the maintenance of a minimal weight for height and a critical percentage of body fat.^{17–21}

To our surprise, more than half of the adolescent female participants who were evaluated as part of ongoing clinical trials reported menarche. Affected girls had extremely low body fat according to clinical observation as well as DXA measurement, and remained prepubertal or progressed only into the early stages of puberty. Menarche was observed in the face of undetectable leptin levels, in line with their low percentage body fat.^{4,22} Normally, leptin is an important pubertal mediator, the product of the *obese* gene produced by fat cells. Leptin is permissive for pubertal advancement at the hypothalamic level by modulation of the gonadotrophic releasing hormone system, although it has also been shown to have effects at other levels of the hypothalamic-pituitary-gonadal axis.²³ Although menarche is typically an event that occurs in girls who are beyond Tanner stage III with regard to breasts as well as pubic hair,²⁴ all participants within the current sample reported menarche while exhibiting no more than Tanner stage II pubertal development and in most cases, Tanner I. Three adolescents started menstruation before their first on-site trial visit, whereas 6 started after trial enrollment. Because the age of menarche was similar among these patients, we infer that the treatments offered through the clinical trials did not influence the onset of menarche.

Consideration of other chronic disease models provides insight into what might be occurring in adolescent girls with HGPS. Anorexia nervosa is a disease characterized by loss of weight and extreme subcutaneous fat loss due to decreased intake because of body image distortion, both of which ultimately contribute to early bone loss in these patients.^{25,26} A number of investigators have identified mean thresholds associated with the re-establishment of menses in girls with anorexia nervosa on the basis of estimates of percentage body fat using height and weight measurements,¹⁸ percentage of ideal body weight,²⁷ and body mass index.²⁸

However, classic early studies have shown that return of menses does not show a simple relationship to weight or body fat,²⁹ although most patients resume menstruation when weight has returned to at least 90% of ideal.³⁰ There are other pediatric chronic diseases such as celiac disease and inflammatory bowel disease that might also result in weight loss, changes in body composition, and delayed puberty at presentation.^{31,32} A better understanding of the complex relationship between weight and menstrual function may shed light on the pathophysiology present in girls with progeria.

The radiographic and biochemical findings in the current group of adolescent girls with HGPS are also not consistent with a primary ovarian disorder such as primary ovarian insufficiency. Interestingly, bone age was normal in more than half of the current participants with only 2 participants exhibiting a delay.^{15,16} In adolescent girls with primary ovarian insufficiency, a delayed bone age would be expected, consistent with primary hypogonadism.³³ The radiographic findings (ie, pattern or normal to advanced bone age) in this and our previous studies is of high interest because of the minimal or lack of pubertal development noted in participants from all of our clinical trials.

Limitations merit consideration and discussion. The median age of the group of patients who did not experience menarche was significantly younger by almost 3 years than those who menstruated. Thus, some girls within this group might go on to experience menarche at a later time. In addition, the observation of menarche in many of our female trial participants was unexpected, and therefore, we did not power our trial to examine the factors that might underlie this observation. Full menstrual histories—including detailed data on frequency, regularity, and approximation of flow volume—were not routinely collected. However, from available data, at least 2 participants reported regular cycles with heavy bleeding. Additionally, although most participants were seen at the study site every 6 months and underwent a full physical examination, the data were sometimes obtained via phone, when families were not able to travel. Therefore, these data could have been less accurate and subject to recall bias. Another limitation is the fact that the findings from physical examinations were not consistently obtained immediately at the time of menarche, nor were participants followed up to adulthood. Future studies should rigorously investigate the anthropometric, hormonal concentrations, disease-related and genetic factors that might explain this observation, including follicle stimulating hormone, anti-Müllerian hormone, and estradiol measurements. Estradiol is among an array of pubertal hormones that mediates growth acceleration, working in concert with growth hormone and insulin-like growth factor I (both which have been shown to circulate in normal concentrations in children and adolescents with HGPS).³⁴ Of interest in this clinical population, estradiol is derived in part from aromatization of androgens in adipose tissue.³⁵ In addition, pelvic ultrasonography to assess ovarian morphology would also be helpful in future studies because we cannot rule out the presence of transient, intermittent, estrogen-secreting ovarian cysts in these patients, which might cause vaginal bleeding.

In summary, menarche was reported in more than half of female clinical trial participants with HGPS. Those with menarche and those without were not different with respect to size, body fat percentage, Tanner stage, or serum leptin concentrations. Participants attaining menarche did not follow the usual pattern of pubertal progression, because menarche was

not preceded by advancement to Tanner IV breasts, gain in body mass, or the expected increase in body fat.²⁴ Progression to menarche was variable; some adolescents started menstruation at Tanner stage I without progression to Tanner II; others started at Tanner stage II. Although there is no record of pregnancy in the literature for any girl with HGPS, the data presented herein suggest the potential for further sexual development in these patients. It will be important to consider menarche, regular menstruation, and Tanner staging of pubertal development as potential disease biomarkers and treatment efficacy measures in future clinical trials.

Acknowledgments

We are extremely grateful to the children with progeria who participated in these studies, as well as their families. We also thank Michele Walters, MD, for her assistance with interpretation of the bone age data.

Clinical trials were supported by The Progeria Research Foundation grants PRFCLIN2007–01, PRFCLIN2009–02, and PRFCLIN2009–03; National Heart, Lung and Blood Institute grant 1RC2HL101631–0; and the Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Awards MO1-RR02172, UL1 RR025758–01, and UL1 TR001102).

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Table 1

Characteristics of Female Participants with HGPS Older than Age 12 Years

Patient ID	Age at last Contact, years	Age at Menarche, years	Testing in Relation to Menarche, months	Tanner Stage for Presence of Sparse Pubic Hair	Tanner Stage for Presence of Breast Bud	Segmental height, cm	Fasting Weight, kg	BMI, kg/m ²	Percentage of body fat by DXA	Leptin, ng/mL	Albumin, g/dL (years)*	Bone age
1	15.8	15.4	12 Pre	1	1	117.8	14.4	10.4	19.8	0.4	4.6 (12.6)	WNL
2	15.2	15.6	12 Pre	1	1	111.6	12.3	9.9	17.7	0.4	4.3	WNL
3	15.75	15.75	24 Pre	1	1	107.8	13.8	11.9	23.1	0.4	4.1 (12.4)	Advanced by 0.4 years
4	16.5	16.5	27 Pre	1	1	112.1	12.9	10.3	20.4	0.4	4.1	WNL
5	13.8	13.3	4 Post	1	2	121.5	16.3	11.0	19.5	0.4	4.2	Advanced by 1.4 years
6	17.4	14.0	6 Post	1	1	107.4	12.1	10.5	15.8	0.5	4.3	Advanced by 0.4 years
7	17.3	14.25	10 Post	2	1	114.3	12.4	9.5	19.4	0.5	4	WNL
8	20.3	14.4	22 Post	1	1	116.2	14.3	10.6	9.3	0.5	3.9	Delayed by 1.4 years
9	19.2	12.0	66 Post	2	2	104.2	13.0	12.0	19.4	0.4	N/M	WNL
A	13.6	–	–	1	1	109.6	13.4	11.2	21.1	0.4	4.3	Advanced by 1.8 years
B	12.8	–	–	1	1	104.6	11.4	10.4	17.6	0.4	N/M	WNL
C	15.25	–	–	1	1	103.8	10.3	9.6	19.8	0.4	4.1 (10.8)	Advanced by 2.0 years
D	14.4	–	–	2	2	116.8	14.2	10.4	20.0	0.4	4.8 (13.5)	WNL
E	12.8	–	–	1	1	102.5	11.5	10.9	18.7	0.4	N/M	WNL
F	17.5	–	–	2	1	113.3	12.1	9.4	15.6	0.4	4.5 (14)	Delayed by 0.1 years

BMI, body mass index; DXA, dual-energy x-ray absorptiometry scan; HGPS, Hutchinson-Gilford progeria syndrome; N/M, not measured; post, after menarche; pre, before menarche; WNL, within normal limits for age.

* When albumin was measured earlier than listed time of testing, age of measurement is listed with albumin value.