Pubertal Height Velocity and Associations with Prepubertal and Adult Heights in Cystic Fibrosis

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Objectives To test the hypothesis that pubertal peak height velocity (PHV) in cystic fibrosis (CF) has improved and is influenced by prepubertal growth and genetic potential.

Study design PHV from 1862 children born in 1984-87 and documented in the 1986-2008 US CF Foundation Registry was determined by statistical modeling and classified into normal, delayed (2-SD > average age), attenuated (magnitude <5th percentile), or both delayed and attenuated (D&A). Genetic potential for height was estimated by parental stature.

Results PHV averaged 8.4 cm/year at age 14.0 years in boys and 7.0 cm/year at age 12.1 years in girls, ~6-month delay and ~15% reduction compared with healthy children. PHV was normal in 60%, delayed in 9%, attenuated in 21%, and D&A in 5%. Patients with delayed PHV reached similar adult height percentile (boys: 34th, girls: 46th) to those with normal PHV (boys: 33rd, girls: 34th); both were significantly taller than the attenuated (boys: 11th, girls: 19th) and D&A PHV subgroups (boys: 8th, girls: 14th). Pancreatic-sufficient patients had taller prepubertal and adult heights but similar PHV compared with pancreatic-insufficient or meconium ileus patients. Adjusting for genetic potential reduced adult height percentiles more in boys (from 25th to 16th) than girls (from 28th to 24th). Height at age 7 years, PHV age and magnitude, and parental stature significantly predicted adult height.

Conclusions Pubertal PHV has improved in children with CF born after mid-1980s compared with older cohorts but remains below normal. Suboptimal prepubertal and pubertal growth led to adult height below genetic potential in CF. *(J Pediatr 2013;163:376-82)*.

Adolescence is a critical period of accelerated height growth. Children with chronic diseases that increase nutritional requirements such as cystic fibrosis (CF) are at high risk for impaired pubertal growth.[1] Results from previous studies[2-11] confirmed the clinical observation that children with CF had delayed and attenuated (D&A) pubertal growth compared with healthy children. However, the majority of these studies were conducted in the 1980-90s using data from children with CF born prior to 1970s,[2-8] and few were from the US.[2,4,5,11]

With advances in new therapies, such as enteric-coated pancreatic enzymes[12-14] and comprehensive nutrition management that emphasizes high-calorie, high-fat diet and growth monitoring,[15-20] pubertal growth in children with CF born after the 1980s may have improved, although recent studies still report impaired pubertal growth.[9-11] Most importantly, critical factors of pubertal growth such as prepubertal growth and genetic potential for height[21,22] have not been carefully evaluated.

The scarcity of studies of pubertal growth in CF is likely attributable to the lack of longitudinal and frequent height data available throughout adolescence and the difficulties in accurately determining the age and magnitude of peak height velocity (PHV). The former is required in order to capture non-linear and seasonal variation in height velocity (HV). The latter is best achieved by using appropriate statistical methods to avoid errors in HV interpolated or extrapolated from adjacent height measurements. Hence, we conducted the present study by utilizing the US CF Foundation (CFF) Registry[23] and a novel semi-parametric growth curve model[24] to estimate PHV from ~1800 children born after the mid-1980s, a period coinciding with increasingly emphasized nutritional care, to test the hypothesis that pubertal PHV in children with CF has improved and is influenced by prepubertal growth and genetic potential.

Methods

The CFF Registry documents the diagnosis and follow-up evaluations of patients with CF seen at accredited centers in the US.[23] Height data were reported annually before 1993 and quarterly after 1994. Therefore, patients born in 1984-1987 would have quarterly height data from 1994

BMI	Body mass index
CF	Cystic fibrosis
CFF	CF Foundation
D&A	Delayed and attenuated
HV	Height velocity
MI	Meconium ileus
PHV	Peak height velocity
PI	Pancreatic insufficiency
PS	Pancreatic sufficiency

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(at age 7-10 years) and reached adulthood by 2008, the most recent year of CFF Registry data available for this study. Of the 4198 born in 1984-1987, 309 died, 951 were lost to follow-up before age 18 years, and 1076 had <3 height measurements per year during age 10-18 years. The remaining 1862 patients were included. This study population did not differ significantly from those excluded from the analysis on sex (boys: 52.9% vs 52.6%, $P = .85$) and prepubertal height percentile at age 7 years (22nd vs 23rd, $P = .20$). The study protocol was approved by the human subjects committee at the University of Wisconsin–Madison.

Growth Curve Modeling to Identify PHV

A semi-parametric shape-invariant model developed by Lindstrom was used.[24] Conceptually, this method assumes that all individuals of the same sex have a common shape for their age versus height curve, which is estimated using data from all children by a non-linear mixed effects model with regression spline that has 2 continuous analytical derivatives. Each child's individual height curve is then determined by shifting and scaling this common curve to obtain the best fit for his/her data. Once an individual's height curve is fitted, the calculated first derivatives of this curve are used to determine the HV curve. Using this approach, 4 measurements characterizing pubertal growth for each child are identified: age at take-off, height at take-off, age at PHV, and magnitude of PHV (Figure 1).

Defining Delayed, Attenuated, and D&A PHV

Longitudinal standards of PHV for North American children developed by Tanner and Davies[25] were used to define normal PHV because they provide reference values for children with different growth tempo (Figure 2). Delayed PHV was defined as PHV age at 2 SD later than average, namely, after 15.3 years in boys and 13.3 years in girls; attenuated PHV was defined as PHV magnitude below the 5th percentile (Figure 2). Using these criteria, PHV was classified into normal (PHV neither delayed nor attenuated), delayed (PHV delayed but not attenuated), attenuated (PHV attenuated but not delayed), and D&A.

CF Phenotypes and Prepubertal Nutritional Status

Meconium ileus (MI) was retrieved from the CFF Registry. Because more than one-quarter of patients (28.7%) were not genotyped, pancreatic insufficiency (PI) and pancreatic sufficiency (PS) were defined by whether or not pancreatic enzymes were used, although this approach may have misclassified ~10% of patients as PI rather than PS because fecal elastase-1 was not available to define pancreatic functional status.[26] Growth at age 7 years was used to reflect prepubertal nutritional status, as the age of PHV take-off in healthy girls with early PHV was 6.5 years[25] and none of the children with CF in our study entered PHV before age 7 years. Growth at age 7 years was indicated by height and body mass index (BMI) z-scores and percentiles, calculated using the 2000 Centers for Disease Control growth charts.[27]

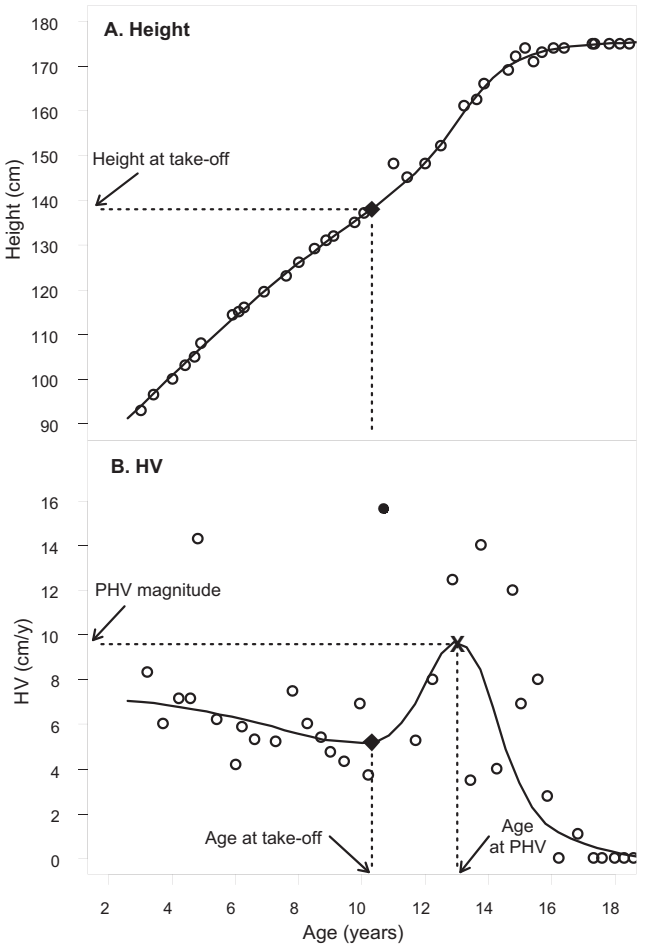

Figure 1. An example illustrating **A,** height curve of a child with CF and **B,** HV curve derived by the semi-parametric, shape-invariant model.[24] Point "x" denotes the PHV magnitude derived from this modeling. Point "•", the largest Y-axis value of all *open circles*, denotes PHV magnitude calculated from 2 adjacent heights.

Adjusting for Genetic Potential for Height

The genetic potential for height was estimated from parental stature using the method of Himes et al[28] validated for CF.[21] This method does not directly predict the child's genetic potential for height but eliminates the influence of tall and short parental stature by generating an "adjusted height" that represents the child's height as if his/her parents had average stature.[28] The following steps are used to calculate Himes adjusted height: (1) calculate mid-parental height; (2) find the Himes adjustment value[28] based on the child's sex, age, height, and mid-parent height; and (3) apply the adjustment value to the child's height to obtain adjusted height.

Of the 1862 patients, 269 (14.4%) had self-reported parental height data documented in the CFF Registry. This subsample did not differ significantly from those without parental height data on sex (boys: 53.2% vs 54.0%, $P = .81$), height percentile at age 7 years (23rd vs 24th, $P = .81$), and adult